Radiation-induced xerostomia in head and neck cancer patients

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Chapter 1

General introduction

Introduction

In the Netherlands, approximately 2000 persons develop a tumour in the head and neck region each year and about 600 patients die of these tumours.[1] The head and neck region harbours numerous delicate organs not only essential for basic physiologic functions as speech and eating, but also for a person's appearance and expression. Therefore, besides the consequences with regard to tumour control and life expectancy, cancer arising in this area and the treatment against these tumours will have a strong impact on many aspects of patient's quality of life.

Most head and neck cancers (> 90%) originate in the mucosal tissues and are squamous cell carcinoma of varying degrees of differentiation. Less frequently, other histological tumour types are found such as adenoid cystic carcinoma and adenocarcinoma arising from salivary gland tissue, malignant melanoma, lymphoma and primary tumours arising from bone, soft tissue and skin. This thesis will focus on squamous cell carcinoma arising from the oral cavity, oropharynx, hypopharynx and larynx.

Treatment

The majority of patients with squamous cell head and neck cancer presents with locally advanced disease. The main reasons for treatment failure are local and/or regional recurrence. Distant metastases occur less frequently.[2]

Radiotherapy and surgery are the main treatment modalities in patients with head and neck cancer. For the majority of patients with limited disease, single modality treatment (surgery or radiotherapy) is sufficient.[3,4,5,6,7,8] Patients with more advanced disease are usually treated with a combination of surgery and postoperative radiotherapy.[9,10,11,12,13,14] Recent studies showed that the addition of concomitant chemotherapy in the postoperative setting improves loco-regional tumour control as well as the overall survival, in particular in case of high risk factors for loco-regional recurrence, including positive surgical margins and lymph node metastases with extra nodal spread.[15,16,17,18,19,20,21,22,23] The last decades, numerous attempts have been made to improve the outcome of these patients and/or to preserve organ function. These include the combination of radiotherapy with chemotherapy,[18,19,20,21,22,24] optimised radiation schedules including hyperfractionation,[25,26] acceleration[26,27,28,29,30] or the combination of hyperfractionated and accelerated radiotherapy.[31] Nowadays, concomitant chemoradiation is regarded standard in the unresectable cases.

Toxicity

Treatment for tumours originating in the head and neck area usually causes acute and late side effects. These side effects depend on a number of factors, such as the location of the tumour and the type and intensity of treatment. After surgery alone, functional and cosmetic problems may arise as well as pain and wound healing problems.[32,33] Radiotherapy on the head and neck area causes acute and late symptoms in virtually all patients. Acute toxicity develops during the course of irradiation and subsides in a few weeks after completion of therapy. The most frequently reported acute problem is mucositis giving rise to pain and an increased risk of bacterial and fungal infections,[34] leading to swallowing difficulties and subsequent weight loss. Other acute radiation-induced side effects include acute dermatitis, reduced taste and smell, sticky saliva and hoarseness.[35] Generally, the degree of acute toxicity is increased with more intense radiation schedules such as hyperfractionation, acceleration and the combination of hyperfractionated and accelerated radiotherapy.[31,34,36] Also, the combination of irradiation with (concomitant) chemotherapy increases acute toxicity.[19,23,34,37] Furthermore, chemotherapy by it self may lead to additional side effects such as mucositis, nausea and vomiting, hair loss, renal toxicity, ototoxicity and bone marrow depression.[31,38,39]

Late radiation-induced toxicity has been defined as side effects developing at least three months after completion of radiotherapy.[40] The most frequently reported late side effect of radiation is xerostomia, which has also been reported as the most serious problem.[41,42,43] Other late sequelas include fibrosis, trismus, (osteo) radionecrosis and functional problems as dysphagia and impaired speech.[44,45]

Xerostomia

Saliva is produced by the major and minor salivary glands lining the oral cavity: the parotid glands, the submandibular glands, the sublingual glands and the minor glands in the oral mucosa. In unstimulated conditions mainly the submandibular glands are responsible for saliva excretion: 65% of the total amount of saliva excreted is derived from the submandibular glands, 20% from the parotid glands, 7-8% from the sublingual glands and 10 % from the minor salivary glands. However, after stimulation, the relative contribution of the salivary glands changes drastically with the parotid glands accounting for over 50% of total saliva.[46,47] The composition of saliva varies depending on the relative contribution

of the salivary glands. Saliva excreted by the parotid glands has higher watery content, whereas the minor salivary glands secrete saliva rich in mucins and the submandibular/sublingual glands secrete saliva with mixed serous/mucous content.[47,48]

Xerostomia includes the objective reduction in the salivary output and changes in its composition and the subjective sensation of dry mouth. Saliva plays an important role in mastication, digestion, swallowing and speech. It protects oral tissues from bacterial infections and inhibits enamel decalcification. Changes in composition may lead to complaints of sticky saliva. A reduced salivary output may thus lead to numerous other side effects which may have a negative impact on the more general dimensions of quality of life (QOL).[49] This becomes clear when listening to patients: they are not understood when talking, have difficulties with eating in company of other people, long for their favourite food but experience a different taste, complain of insomnia, etcetera.

Radiation-induced xerostomia

Morphologically, it has been observed in primates[50] and rats[51] that the effects of irradiation of the salivary glands are most evident in serous cells. In rhesus monkeys, acute degeneration and necrosis of the serous cells were observed after 24 hours after irradiation and the effect was dose dependent. The predominant histopathological change observed after 16 or more weeks after irradiation was atrophy caused by a lack of serous acini, implying a lack of replacement of the functional serous cells that were lost within a few days following irradiation. In rats, it was reported that the effect of irradiation on salivary glands consists of four phases: acute glandular function damage, followed by progressive cell loss, a stable phase and a phase of an attempt to restore damage by stem cells.[52,53] Dynamic investigations by scintigraphy in patients treated with irradiation for head and neck malignancies suggests that shortly after irradiation xerostomia is based predominantly on the failure of the gland to excrete saliva, whereas later on, a decreased trapping ability together with a loss of secretory function plays a role.[54] The initial loss of the watery content relative to the mucins leads to the development of sticky saliva. Over time, also the mucinous cells are affected and the sticky saliva may disappear.

Although it is clear that radiation to the head and neck area causes xerostomia, the relation between irradiation and xerostomia is still under investigation. Submandibular glands seem more sensitive to

radiotherapy than parotid glands as seen in rats,[52] but the clinical significance of this observation remains unknown.

Clinical studies of dose-volume/response relationships in the major salivary glands have primarily focused on the parotid glands. In the 1980's and early 1990's it was already observed that the parotid salivary flow was reduced after including major salivary glands in the radiation fields.[55,56,57] However, these studies were based on 2D-information. For an adequate analysis of the relationship between xerostomia and the irradiated volume and dose to the organs at risk, 3D-information derived from planning-CT scans is required with an accurate delineation of the organs at risk and analysis of the exact dose in these organs by dose-volume histograms (DVH). In recent years, several studies using 3-D information have demonstrated threshold doses for stimulated saliva production varying from 25.8 to 43 Gy for the parotid gland.[58,59,60,61] The common finding in these studies was that the probability of a significant reduction in stimulated salivary flow was best predicted by the mean parotid dose.

Assessing xerostomia

Current available measurements of xerostomia come in several categories: (1) functional imaging of gland activity, (2) measurements of salivary gland output, (3) observer-assessed toxicity grading and (4) questionnaires assessing patient-reported evaluation of quality of life and various xerostomia-related symptoms.

Scintigraphy of the salivary glands yields spatial information of functional activity related to uptake, concentration and excretion of saliva. A relation of gland function and dose distribution within the gland can be made, especially when combined with single-photon emission tomography (SPECT).[62] Scintigraphy results have a reasonable correlation with salivary output measurements,[63,64] but a lack of correspondence with xerostomia-related questionnaires has been reported.[65] Because of its technical complexity scintigraphy has found little way in routine clinical assessment of xerostomia.

Measurements of salivary output are the most commonly applied objective measures of xerostomia. There are several methods to collect saliva: unstimulated and stimulated saliva collections, whole mouth saliva, and selective saliva collection per gland. Stimulated saliva is usually obtained by application of citric acid 2-5% to the lateral side of the tongue. Selective collection of parotid gland saliva is obtained by

application of a suction cup over the orifice of the parotid ducts. Selective collection of the submandibular glands may be performed by selective suction of the gland canals orifices at the floor of mouth. There exists no satisfactory selective way to collect saliva from the minor salivary glands. Production of saliva is dependent on several factors as diurnal variation, the way of salivary gland stimulation, hydration and medication.[66,67,68,69]

Several observer-defined toxicity-grading systems exist to score xerostomia. The most commonly used are the RTOG scoring system,[40] CTC v3.0[70] and LENT SOMA[71] (Table 1). The RTOG scoring criteria of xerostomia are separated in acute and chronic. Acute xerostomia grades (within 3 months after commencing therapy) are defined primarily by symptoms: degree of dry mouth, quality of saliva and taste changes. The chronic xerostomia is ranked according to the degree of mouth dryness and the response to stimulus application.[40] It is not clear whether these are observer-rated or patient-reported. No validation of this grading system has been performed. Also the CTCAE criteria are ranked according to quality of saliva and taste changes. Recently a new version of the CTC grading system has been published, called CTCAE v3.0,[70] incorporating full surgical, late effects and paediatric criteria whereas the CTC v2.0 focused on acute effects.[72] The grading of xerostomia was revised containing now subjective evaluation of dry mouth and objective criteria as changes in oral intake and unstimulated salivary flow rate. The LENT-SOMA scoring system of xerostomia includes subjective grading of dryness, whether it is debilitating or not, objective findings of mucosal moisture, management issues as the frequency of saliva substitutes and the salivary flow relative to pre-treatment flow.[71]

Another way to assess the degree of xerostomia is by means of self-administered questionnaires. In published literature, validated as well as non-validated xerostomia questionnaires are used. Examples of these questionnaires are: the Rotterdam xerostomia questionnaire,[73] the visual analogue scale xerostomia questionnaire (VAS),[74] the Patient Benefit Questionnaire (PBQ)[75] and the xerostomia questionnaire (XQ) developed by Eisbruch et al.[76] No clear correlation has been observed between salivary flow rate and subjective xerostomia scores.[35,56,76]

Table 1. Commonly used toxicity grading systems for xerostomia.

Toxicity scoring system	Grading					
	0	1	2	3	4	5
RTOG: acute (< 90 days after irradiation) [40]	No change over baseline	Mild mouth dryness/slightly thickened saliva/may have slightly altered taste such as metallic taste/these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/thick, sticky saliva/markedly altered taste	-	Acute salivary gland necrosis	-
RTOG: late (> 90 days after irradiation) [40]	None	Slight dryness of mouth, good response to stimulation	Moderate dryness of mouth, poor response to stimulation	Complete dryness of mouth, no response to stimulation	Fibrosis	Death related to salivary gland injury
CTC v AE 3.0 [70]	-	Symptomatic(dry or thick saliva) without signifcant diet alteration: unstimulated saliva flow >0.2 ml/min	Symptomatic and significant oral intake alteration(e.g. copoius water, other lubricants diet limited to purees and/or soft, moist foods): saliva flow 0.1- 0.2 ml/min	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings or TPN indicated; saliva flow >0.2 ml/min	-	-
SOMA LENT [71]	None	Occasional dryness; normal moisture; no mangement for symptoms; salivary flow 76-95% of pretreatment	Partial but persistent dryness; scant saliva; occasional saliva substitutes, sialogogues; salivary flow 51-75% of pretreatment	Complete dryness, non-debilitating; absence of moisture, sticky, viscous saliva; frequent saliva substitutes, sialogogues; salivary flow 26-50% of pretreatment	Complete dryness, debilitating; absence of moisture,coated mucosa; needs saliva substitute or water in order to eat, sialogogues; salivary flow <26 % of pretreatment	-

Treatment and prevention of xerostomia

Though spontaneous recovery from radiation-induced xerostomia in head and neck cancer patients has been reported,[77] many patients remain suffering from xerostomia after treatment.[43] Therefore, treatment and prevention of radiation-induced xerostomia is an important issue for physicians treating head and neck cancer patients. In patients suffering from xerostomia due to various causes the application of salivary substitutes has been tried for a long time. Many salivary substitutes have been developed, containing ingredients to duplicate the rheological properties of saliva. Saliva substitutes may relieve symptoms to some extend, yet, in most cases they were found unsatisfactory by patients.[78,79,80,81]

Administration of pilocarpine is another method to reduce the effect of radiation on xerostomia. This drug stimulates saliva secretion by acting on the muscarinic receptor. For full effect some residual function of the salivary gland after radiotherapy is necessary. In clinical studies, pilocarpine may produce some symptomatic improvement.[82,83] However, in the majority of cases, xerostomia remains an important symptomatic side effect.

With the implementation of Intensity-modulated radiotherapy (IMRT) in daily practice, increasing attention is paid to the prevention of radiation-induced xerostomia with this new technique. The parotid glands can be significantly spared with most IMRT techniques, though at the cost of a higher dose in the oral cavity.[84,85] Various studies have shown a reduced mean dose to the parotid gland below 26-39 Gy, leading to an increased number of patients with a retained stimulated salivary flow of $\geq$ 25% of the pre-radiation flow rate.[59,60] However, concurrent sparing of the submandibular glands responsible for saliva production in unstimulated conditions (rest) with this technique remains difficult.[86] Hence, it is interesting that Jha et al. reported on a prospective study in which the submandibular salivary glands were surgically transferred to the submental space in order to prevent radiation-induced xerostomia.[87]

Another way to prevent radiation-induced xerostomia is to increase the therapeutic ratio by enhancement of the radioresistance of normal tissues, without inducing protection of the tumour to radiation. Preclinical data supported that Amifostine could possibly be used as radioprotector because its radioprotective properties in normal tissues turned out to be higher compared to tumour cells.[88] Amifostine is a thio-organic compound that was originally developed as a protector against

radiation-induced toxicity in the event of nuclear war. The mechanism of selective radioprotection in normal tissues is multi-factorial.[89,90] First, the inferior blood supply in tumours may result in less delivery of Amifostine as compared to normal tissues. Second, Amifostine does not have a protective activity by itself. The compound is activated through dephosphorylation to the free-thiol WR-1065. The sulfhydryl group on the active form WR-1065 acts as a radioprotective agent by scavenging free radicals and donating a hydrogen atom to facilitate repair. The generation of the free thiol WR-1065 is catalysed by plasma membrane-bound alkaline phosphatase. It has been demonstrated that normal tissues have a high concentration of alkaline phosphatase; especially at the capillary level and after conversion of Amifostine to WR-1065 there is a rapid uptake into normal tissues.[90] Recently it has been shown that the specific activity of membrane-bound alkaline phosphatase is 275-fold higher in normal cells than in non-small cell lung cancer cells.[91] Furthermore, the neutral pH environment of normal tissues as compared to the acidic pH found in many tumours favours the preferential enzymatic action of alkaline phosphatase in normal tissues.[90]

Amifostine and its active metabolite, WR-1065, accumulate in many epithelial tissues with the highest concentrations found in the salivary glands, spleen and kidneys.[92] There are a number of normal tissues, which have been reported to be protected, particularly the salivary glands. In tumour bearing animals, there was a selective cytoprotection of normal tissues from the irradiation without protection of the tumour.[93,94,95] Small clinical trials have suggested that Amifostine protects against radiation-induced xerostomia and mucositis.[96,97,98] Brizel and co-workers[99] conducted a large, prospective randomised multicenter trial for patients treated with radiotherapy for head and neck cancer. Patients were randomized to receive radiotherapy alone versus radiotherapy plus Amifostine (200 mg/m^2 i.v. over 3 minutes) during the course of radiotherapy. The incidence of grade $\geq$ 2 acute xerostomia decreased from 78% without Amifostine to 51% with Amifostine ($p<0.001$), while the median dose at onset of xerostomia was 42 Gy without Amifostine and 60 Gy with Amifostine ($p=0.0001$). After two years, no significant difference on survival or tumour control was observed. Since the administration of Amifostine during radiotherapy is labour and cost intensive, it could be worthwhile to investigate whether other than daily administration schemes are effective as well regarding the prevention of xerostomia.

Quality of life in head and neck cancer patients

No uniform definition of health-related quality of life exists: generally it refers to the patient's perception of the impact of illness on general well-being and satisfaction. It is defined by the WHO as follows: "An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, standards and concerns. It is a broadening concept affected in a complex way by the person's physical health, psychosocial state, level of independence, social relationships and their relationships to salient features of their environment."[100] Major health-related dimensions include physical, occupational, social and psychological dimensions. To assess quality of life it is important to stress the subjective experience of the person whose quality of life is in question. In this thesis, the term quality of life (QoL) is used as a synonym for health-related QoL.

Validated generic measures are available to assess quality of life in general in cancer patients, e.g. EORTC QLQ-C30,[101] Short form survey (SF-36),[102] FACT-G[103] the QoL-radiation therapy instrument[104] and the Rotterdam symptom checklist.[105] These questionnaires are not interchangeable. Although they all measure some aspects of quality of life, they provide different information. Furthermore, several head and neck specific quality of life questionnaires were developed. They include: the EORTC QLQ-H&N35,[101] used in conjunction with EORTC QLQ-C30, FACT H&N,[106] University of Washington questionnaire (UW-QOL),[107] the QoL-radiation therapy instrument- Head and neck module,[108] the QoL questionnaire for advanced head and neck cancer,[109,110] the head and neck radiotherapy questionnaire[110] and the performance status scale for head and neck cancer (PSS-HN).[106] These questionnaires, whether focused on assessing general QoL or disease specific QoL, vary widely in their methodology, strengths and weaknesses. Some are applicable for all (head and neck) cancer patients; some are specifically designed for surgically treated head and neck patients (UW-QOL), others for patients treated with radiotherapy (e.g. the QoL-radiation therapy instrument and supplemental module and the head and neck radiotherapy questionnaire). Some of these questionnaires are well validated, while for others this process is still ongoing. They also vary in the items being investigated. Therefore, no ideal questionnaire for all purposes exists.

In this thesis, it was decided to use the EORTC QLQ-C30 questionnaire together with the head and neck specific module QLQ-H&N35 to asses the relation between xerostomia and QoL and related domains

because it is well validated, being applicable in multicultural settings, widely used in international research and it has been translated for use among Dutch patients. The EORTC QLQ-H&N35 questionnaire is a self-administered questionnaire and includes symptoms (xerostomia, teeth, sticky saliva, trismus, senses, cough and pain) and scales concerning social eating, social contact, swallowing difficulties, speech problems. It seems to be sensitive to temporal changes before, during and after treatment with surgery, radiotherapy and chemotherapy.[111]

Aim and outline of this thesis

As pointed out in the introduction, xerostomia is an important problem after radiotherapy in head and neck cancer patients. This thesis focuses on subjective xerostomia; its impact on quality of life, factors associated with the risk of developing dry mouth and two studies on prevention and treatment.

Though it is often assumed that increasing morbidity affects quality of life negatively, little is known about the effect of radiation-induced xerostomia on QoL and related dimensions. In chapter 2, the impact of radiation-induced xerostomia on general quality of life measures and related parameters after primary radiotherapy in head and neck cancer patients is described.

Furthermore, though the relation between the parotid gland and dry mouth has been studied intensively, still several questions on the risk of developing radiation-induced xerostomia remain. First, what is the role of the other salivary glands on the risk of developing xerostomia as experienced by patients and is there some interaction between these factors in bilaterally treated patients (Chapter 3)? Second, since radiation technique for head and neck tumours is continuously changing due to new insights and new available techniques like IMRT, could results obtained from patients treated with bilateral irradiation be translated to patients treated with other treatment techniques, e.g. unilateral irradiation? In chapter 4, the risk of developing xerostomia in unilaterally treated patients is studied in comparison to bilaterally treated patients. And third, now combined modality is more and more used for patients with advanced disease, what is the impact of the addition of chemotherapy to irradiation on the risk of developing radiation-induced xerostomia (chapter 5)?

In addition, in two randomised studies attention is paid to the prevention (Amifostine, chapter 6) and treatment of radiation-induced xerostomia

(Xialine®; chapter 7).

Finally, the results of our findings will be discussed in chapter 8.

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Chapter 2

The impact of radiation-induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer

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Abstract

Purpose: to investigate the impact of xerostomia on overall quality of life (QoL) outcome and related dimensions among head and neck cancer patients treated with primary radiotherapy.

Patients and methods: 288 patients with stage I-IV disease without distant metastases were included. Late xerostomia according to the RTOG (RTOG-xerostomia) and QoL (EORTC QLC-C30) were assessed at baseline and every 6th month from 6 months to 24 months post-radiotherapy.

Results: A significant association was found for RTOG-xerostomia with overall QoL outcome (effect size (ES) 0.07, $p<0.001$). A significant relation with global QoL, all functioning scales and fatigue and insomnia was observed. Between RTOG-xerostomia and sex and between RTOG-xerostomia and age, a significant interaction term was present. RTOG-xerostomia had a larger impact on overall QoL outcome in women (ES women 0.13 vs 0.07 for men). Furthermore, in women ES on individual scales were larger and a marked worsening was observed with increasing RTOG-xerostomia. No different ES according to age was seen (ES 0.10 for 18-65 years vs 0.08 for > 65).

Analysing the impact of RTOG-xerostomia on overall QoL outcome over time showed an increase from 0.09 at 6 months to 0.22 at 24 months. With elapsing time, a worsening was found for these individual scales with increasing RTOG-xerostomia.

Conclusions: The results of this prospective study are the first that showed a significant impact of radiation-induced xerostomia on QoL. Although the incidence of ≥ grade 2 RTOG-xerostomia decreases with time, its impact on QoL increases. This emphasizes the importance of prevention of xerostomia.

Introduction

Radiotherapy is an important treatment modality for head and neck cancer. Radiotherapy as single modality is generally considered standard in early stages (e.g. T1N0M0 glottic cancer), while in the more advanced cases, radiotherapy is combined with surgery and/or chemotherapy.[1,2,3] The most frequently reported late side effect of radiation by patients is xerostomia, which, depending on tumour location, they also reported as the most serious problem after radiation.[4,5,6] There is an increasing interest in the prevention of radiation-induced xerostomia as reduced salivary output may result in problems with mastication, digestion, swallowing and speech, and an increased risk of caries and oral infections.[7,8,9,10,11]

In general, a distinction is made between early and late radiation-induced morbidity. Early side effects occur during or immediately after completion of radiotherapy and subsequently decrease with time. In contrast, late side effects are generally considered irreversible and progressive and are therefore probably more relevant for patients with respect to their quality of life (QoL).

A number of toxicity grading systems have been developed for classifying late radiation-induced toxicity in which grading is ranked according to the severity of a given side-effect. These classification systems include the Subjective, Objective, Management, Analytic/Late Effects Normal Tissue system (SOMA-LENT),[12] the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer system (RTOG/EORTC),[13] and more recently, the Common Terminology for Adverse Events version 3.0 (CTCAE v3.0).[14] The latter toxicity grading system does not only take into account toxicity induced by radiotherapy but also adverse effects induced by other treatment modalities such as surgery and chemotherapy. It is often assumed that because of the ranking depending on the severity of late toxicity, QoL of patients will decrease with increasing rates of morbidity. However, information with regard to the clinical relevance of radiation-induced toxicity in terms of QoL is scarce.

Therefore, the aim of the present study was to investigate the impact of xerostomia on QoL among head and neck cancer patients treated with primary radiotherapy. The hypothesis to be tested was that higher grades of radiation-induced toxicity as assessed by the RTOG Late Radiation Morbidity Scoring System should be associated with worse QoL.

In addition, as the profile of side effects may change over time, we also

investigated whether the impact of xerostomia on QoL changed over time. As a number of studies indicated a gradual reduction of radiation-induced xerostomia over time,[15,16,17] the hypothesis was tested that the impact of radiation-induced xerostomia on overall QoL would decrease over time as well.

Patients and methods

Patients

Patients eligible for this study were those with stage I-IVB[18] head and neck cancer. All patients had a life expectancy of at least 12 months and were treated with primary radiotherapy with curative intent. A good understanding of the Dutch language was required to be able to complete the questionnaire. Excluded were those with distant metastases (M1), previously irradiated patients, patients treated in combination with induction or concurrent chemotherapy and patients with a tumour originating in the salivary glands. From December 1998 to January 2004, 288 patients met the eligibility criteria and completed the baseline questionnaire. The demographic and tumour characteristics of the study population are listed in Table 1. Seventy-seven percent of patients were male. The median age at the start of radiotherapy was 64 years (Range: 25-97 years).

Radiotherapy

Radiotherapy was delivered using megavoltage equipment (6-15 MV linear accelerator). Generally, the initial target volume was irradiated using two opposing lateral fields with an anterior field to cover the lower jugular and supraclavicular lymph node areas.

In case of primary radiotherapy of the more advanced cases that were considered not suitable for chemoradiation, an accelerated schedule with concomitant boost technique was used. These patients were generally treated with 6 fractions a week with a second fraction on Friday afternoon with a minimum interval of 6 hours, to a total dose of 70 Gy in 6 weeks. Elective nodal irradiation was administered to a total dose of 46 Gy and a boost on the primary tumour and pathological lymph nodes to a total dose of 70 Gy.

Table 1. Patient characteristics .

Variable	Number (N=288)	%
Sex		
Female	67	23%
Male	221	77%
Age		
18-65 years	159	55%
>65 years	129	45%
Performance		
WHO-0	109	38%
WHO-1	149	52%
WHO-2	24	8%
WHO-3 & 4	5	2%
unknown	1	0.3%
T-classification		
unknown primary	3	0.3%
T1-2	190	66%
T3-4	95	33%
N-classification		
N0	206	72%
N+	82	28%
Histology		
squamous cell carcinoma	278	96%
undifferentiated carcinoma	10	4%
Site		
oral cavity	17	6%
oropharynx	55	19%
nasopharynx	11	4%
hypopharynx	23	8%
larynx	158	55%
vestibulum nasi	16	5%
other*	8	3%

* nasal cavity 1, maxillary sinus 2, cervical esophagus 2, unknown primary 3.

Assessment of late radiation-induced toxicity

In 1997, we started the Toxicity Assessment Program at the department of Radiation Oncology among all patients with head and neck cancer treated with primary or postoperative (chemo)-radiation. Acute and late radiation-induced morbidity were prospectively assessed according to the RTOG[13] at baseline and subsequently at 6 weeks and with 6 months intervals from 6 months to 24 months after completion of radiation. For the purpose of the present study, only the assessments made after completion of radiation were used.

Assessment of patient-rated Quality of life

For the evaluation of QoL, the EORTC Core Questionnaire (QLQ-C30 v3.0) was used.[19,20,21] The EORTC QLQ-C30 is a cancer-specific QoL questionnaire developed for repeated assessments within clinical trials. It is developed in a cross-cultural setting and has been found valid and reliable for QoL assessments in various cancer populations, including head and neck cancer. It contains five functional scales (physical, cognitive, emotional, social, role), a global QoL scale, three symptom scales (pain, fatigue and nausea/vomiting) and six single items (dyspnoea, insomnia, loss of appetite, constipation, diarrhoea and financial difficulties). All scores on scales and single items are converted to a 0 to 100 scale. A high score for a functional or global quality of life scale represents a high level of symptoms. An EORTC approved Dutch translation of the questionnaire was used.

QoL was assessed at the same time-points on which late-radiation-induced toxicity was assessed.

Statistics

Changes in the mean scores of the QoL scales over time were tested with the paired t-test.

The impact of RTOG-xerostomia on QoL and other dimensions was tested in a multivariate analysis of variance (MANOVA) using the general linear model (GLM). This analysis can be used to test a significant association between a set of interrelated variables (i.e. the QoL scales) and one or more grouping variables (RTOG-xerostomia). It also takes into account the correlation between the dependent variables. Therefore, this statistical procedure was preferred instead of an analysis of each QoL scale separately. This multivariate approach also protects against type I errors.

In the present study, the GLM-MANOVA was performed in three steps. First, to investigate the association of RTOG-xerostomia with QoL, an overall analysis was performed with all data to establish whether RTOG-xerostomia was associated significantly with overall QoL outcome. Wilks' Lambda was used to test the impact of each variable included in the multivariate model on QoL. Wilks' lambda can take values ranging from 0, indicating large differences in group means, and 1 indicating no differences.

In the second step, the influence of possible confounding by other characteristics was studied by adding these factors to the model. Possible interaction (effect modification) by sex (male vs female), age (18-65 years vs > 65 years), UICC stage (stage I vs II vs III vs IV), fractionation (conventional vs accelerated radiotherapy) and tumour site (larynx vs hypopharynx vs oropharynx vs oral cavity vs other) was studied by adding the product terms to the model. Significant factors as well as confounders and interaction terms were added to the final model.

In the third step, after establishing the final model, the association between RTOG-xerostomia and each QoL scale was analysed separately. The presented associations and mean scores were thus corrected for confounding and effect modulation.

The variance in QoL scores sustained RTOG-xerostomia is expressed by the effect size (explained variance). For example, an effect-size of 0.224 indicates that 22.4% of the variance in QoL is accounted for by RTOG-xerostomia.

Subsequently, to analyse the impact of RTOG-xerostomia over time, we performed the same three-step analysis with 6 months interval from 6 months to 24 months. All analyses were performed by using SPSS for WINDOWS (version 11.0; SPSS Inc, Chicago).

Results

Compliance

All 288 patients returned the baseline questionnaire (100%). The compliance at 6 months was 90% (234 out of 260 patients alive), 91% (207 out of 227 patients alive) at 12 months, 91% (181 out of 200 patients alive) at 18 months, and 89% (142 out of 160 patients alive) at 24 months.

Baseline scores and changes in time for xerostomia

Changes of RTOG-xerostomia at the different time points after completion of radiotherapy are presented in Figure 1. Most patients had no xerostomia (96%) at baseline. After radiotherapy, a significant increase in xerostomia was observed with approximately two third of the patients having some degree of xerostomia at 6 weeks. Subsequently, no significant changes were observed.

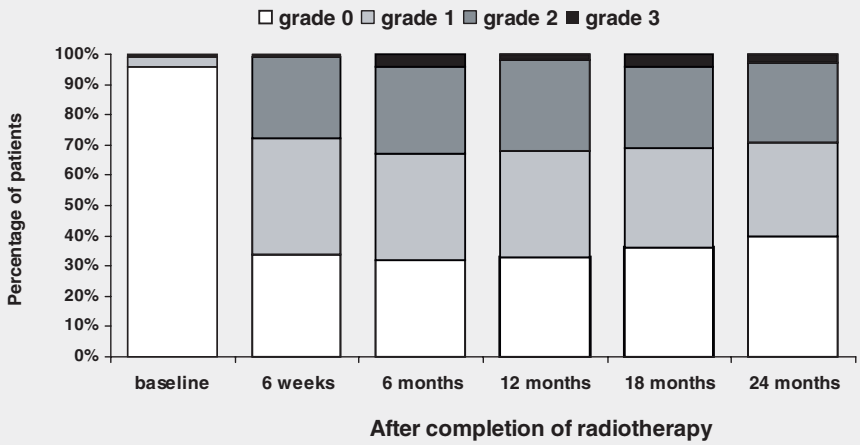

Figure 1: Xerostomia according to RTOG criteria at different time points after completion of radiotherapy.

Impact of xerostomia on QoL and QoL-related dimensions

In the first step of GLM-MANOVA, the association between RTOG-xerostomia and QoL was investigated. In this analysis, the combination of the five functioning scales, the global QoL scale and the general symptoms insomnia and fatigue as assessed with the QLQ-C30 were used as the dependent variables. RTOG-xerostomia was significantly associated with the overall QoL outcome ($p < 0.0001$).

In the second step of GLM-MANOVA, the influence of possible confounding by other characteristics was studied. No confounding was observed when sex, age, UICC stage, fractionation and tumour site were added to the model (not shown). However, age, sex and fractionation were significantly associated with overall QoL, (Table 2). Furthermore, a significant interaction term was present between RTOG-xerostomia and age and between RTOG-xerostomia and sex, indicating that the

Table 2. Univariate and multivariate analysis of the impact of RTOG-xerostomia and other pre-treatment characteristics on overall QoL outcome (EORTC QLQ-C30).

Variable	Wilks' Lambda	Significance	Effect size
Univariate analysis			
RTOG-xerostomia	0.83	< 0.001	0.06
Age	0.90	< 0.001	0.10
Sex	0.95	0.001	0.05
Fractionation	0.97	0.02	0.03
Tumour site		ns*	
UICC-stage		ns*	
Multivariate			
RTOG-xerostomia	0.86	< 0.001	0.05
Age	0.90	< 0.001	0.04
Sex	0.97	0.001	0.03
RTOG-xerostomia * age	0.89	< 0.001	0.04
RTOG-xerostomia * sex	0.92	< 0.001	0.03

* ns means P >0.05

magnitude of the effect of RTOG-xerostomia on QoL depended on age and sex (Table 2).

More detailed analysis showed that RTOG-xerostomia, and sex were significantly associated with all functioning scales and with fatigue and insomnia. Age was significantly associated with physical functioning and fatigue (Table 3).

An additional analysis was performed to get more insight in the clinical relevance of the associations found by estimating the marginal means (EMM) of the QoL dimensions as a function of grade of RTOG-xerostomia. The results are depicted in Figure 2. A decrease in mean score representing worsening of functioning was seen with increasing xerostomia for global QoL and all functioning scales except emotional functioning, while an increase in mean score representing worsening of symptoms was seen for insomnia and fatigue.

Table 3. The impact of RTOG-xerostomia on individual QoL scales (EORTC QLQ-C30).

Variable	xerostomia (RTOG)		Age		Sex	
	effect size	p-value	effect size	p-value	effect size	p-value
Physical functioning	0.08	<0.0001	0.05	<0.0001	0.01	0.01
Role functioning	0.05	<0.0001		ns*	0.01	0.04
Cognitive functioning	0.02	0.03		ns*	0.02	<0.0001
Emotional functioning	0.01	0.08		ns*	0.04	<0.0001
Social functioning	0.06	<0.0001		ns*	0.01	0.02
Global QoL	0.05	<0.0001		ns*	0.01	0.02
Fatigue	0.07	<0.0001	0.01	0.03	0.02	0.001
Insomnia	0.05	<0.0001		ns*	0.02	0.003

* ns means P >0.05

Impact of RTOG-xerostomia according to sex

Because of the interaction term present between RTOG-xerostomia and sex, an additional analysis was performed to investigate the impact of RTOG-xerostomia according to sex. A marked difference was found between men and women: the effect sizes of RTOG-xerostomia for the impact on overall QoL were 0.13 in female and 0.06 in male patients, respectively (Table 4). More detailed analysis showed that the effect sizes of RTOG-xerostomia among female patients were larger for most functioning scales, fatigue and insomnia (Effect sizes: 0.09-0.19) compared to that observed in male patients (Effect sizes: 0.01-0.07).

The impact of the grade of RTOG-xerostomia on the mean scores of the individual QLQ-C30 scales is depicted in Figure 3. In female patients, a marked decrease in mean scores representing worsening of functioning was seen with increasing xerostomia for global QoL and most functioning scales, while a distinct increase in mean score, representing worsening of symptoms, was seen for insomnia and fatigue. In male patients, similar effects were observed but the differences were less pronounced.

Table 4. The impact of xerostomia on overall QoL outcome (C30) according to subgroup.

	Wilks' Lambda	Significance	effect size
xerostomia according to sex			
men	0.82	<0.0001	0.06
women	0.66	0.006	0.13
xerostomia according to age			
18-65 years	0.73	<0.0001	0.1
> 65 years	0.79	0.001	0.08

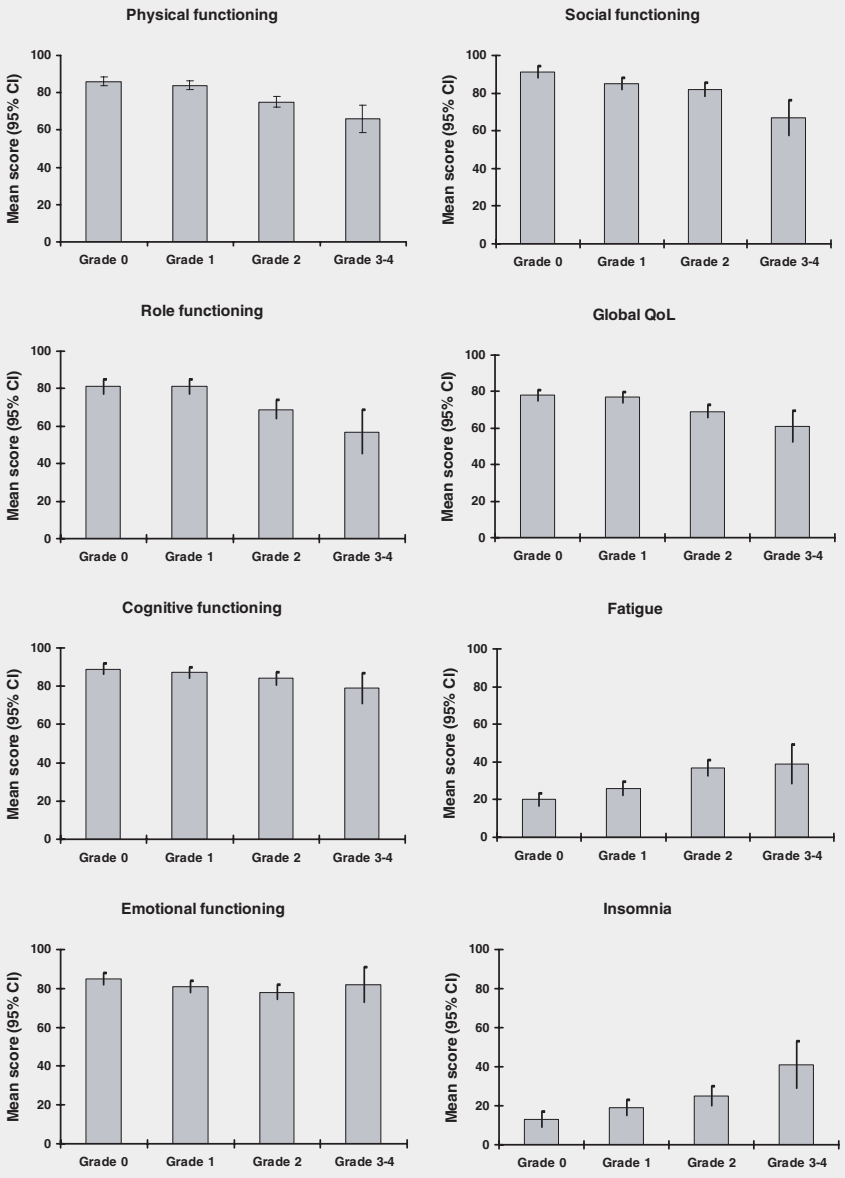

Figure 2: Estimated marginal means of the quality of life scales as a function of RTOG-xerostomia.

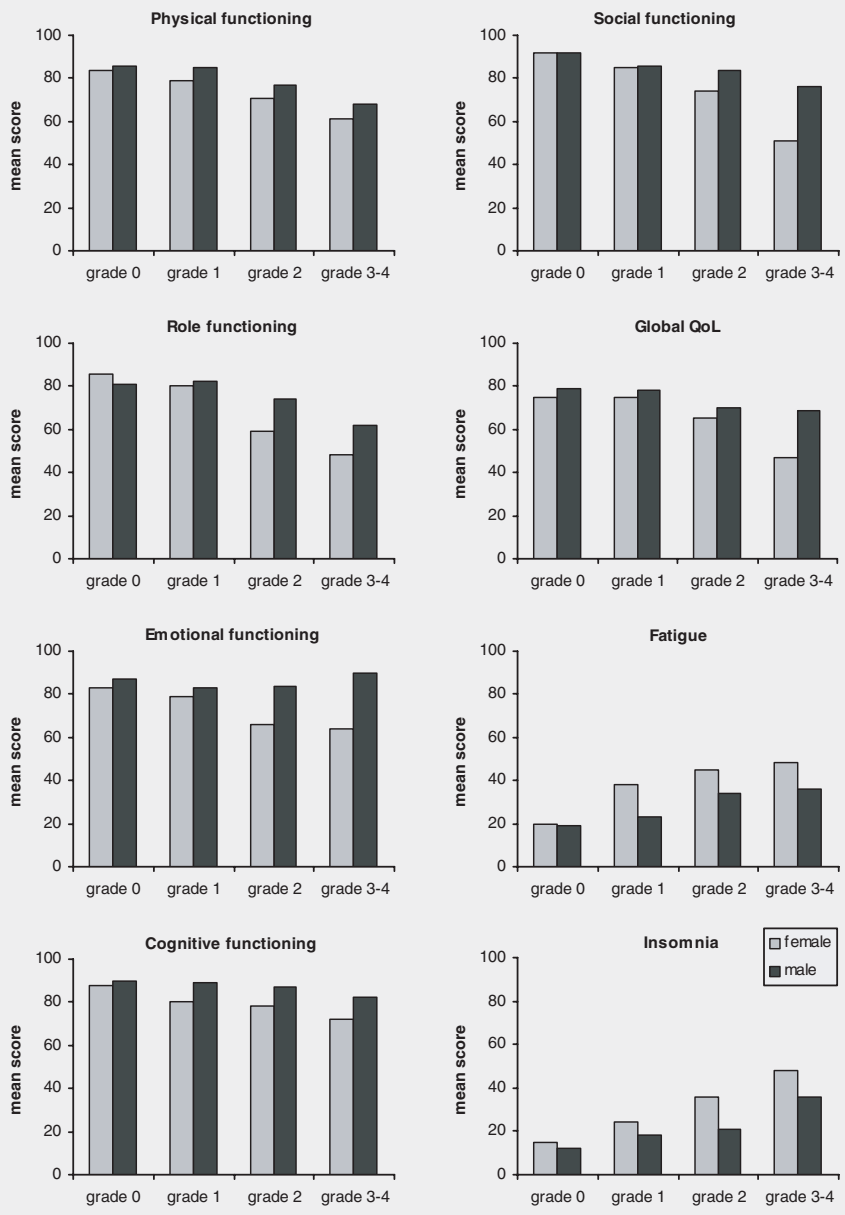

Figure 3: Estimated marginal means of the quality of life scales as a function of RTOG-xerostomia according to gender.

Impact of RTOG-xerostomia according to age

Because of the interaction term present between RTOG-xerostomia and age, an additional analysis was performed to investigate the impact of RTOG-xerostomia stratified by age group. A slight difference was found between the two age categories (18-65 years versus > 65 years). The effect sizes of RTOG-xerostomia for the impact on overall QoL were 0.10 in younger patients and 0.08 in elderly patients (Table 4). More detailed analysis showed that RTOG-xerostomia in both age categories was significantly associated with most functioning scales and with fatigue and insomnia, but the effect was larger for physical and social functioning and insomnia among the younger patients (effect sizes 0.10- 0.11 for younger patients versus 0.05 for older patients), while among elderly patients the effect on role functioning was larger (effect size 0.11 versus 0.05 for younger patients). The results regarding the impact of age on the mean scores of the individual QLQ-C30 scales are depicted in Figure 4. In younger patients, a decrease in the mean scores representing worsening of functioning was seen with increasing grades of RTOG-xerostomia for global QoL and all functioning scales except for emotional functioning, while an increase in mean scores representing worsening of symptoms was seen for insomnia and fatigue. In elderly patients, for physical functioning, role functioning, insomnia and QoL similar effects were observed but the differences were less pronounced. No clear relationship between RTOG-xerostomia score and the mean score on the other QoL related dimensions was observed.

Impact of xerostomia (RTOG) in time

Finally, we investigated whether the impact of RTOG-xerostomia changed with time. At all time points, a significant relation was observed for RTOG-xerostomia with the overall QoL outcome The effect size increased from 0.09 at 6 months ($p=0.003$) and 12 months (n.s.) to 0.19 at 18 months ($p< 0.0001$) and 0.22 at 24 months ($p=0.001$).

More detailed analysis showed that RTOG-xerostomia was generally associated with an increased effect size over time for role and cognitive functioning. No significant effect was observed for the other functioning scales and global QoL, though at 24 months, a large effect size was observed for RTOG-xerostomia on physical functioning, emotional functioning, fatigue and insomnia (Figure 5).

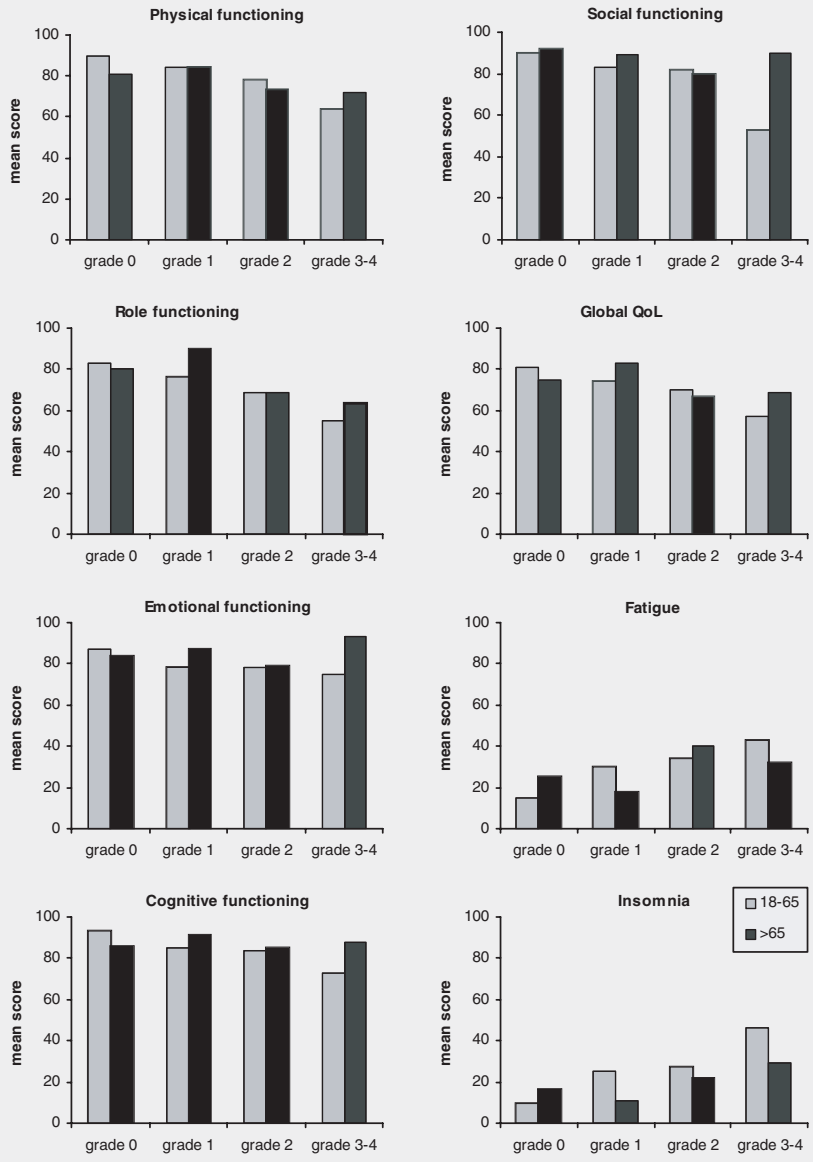

Figure 4: Estimated marginal means of the quality of life scales as a function of RTOG-xerostomia according to age.

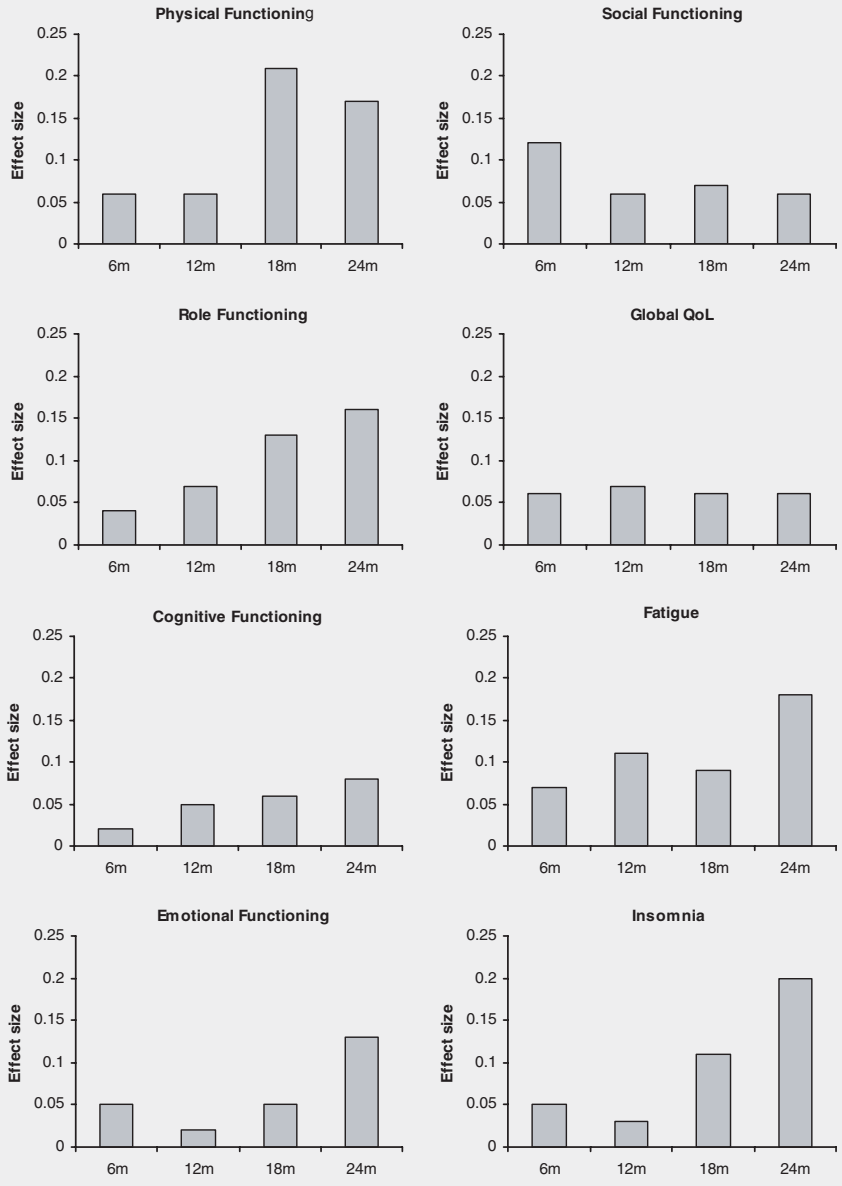

Figure 5: Estimated marginal means of the quality of life scales as a function of RTOG-xerostomia over time.

Discussion

This is the first study investigating the impact of radiation-induced xerostomia on overall QoL outcome. The results indicate that RTOG-xerostomia has a significant effect on different dimensions of QoL. Moreover, the effect of xerostomia on overall QoL outcome increases with elapsing time, even though the incidence of xerostomia decreases.

The tolerance dose for damage to the parotid glands is approximately 26-40 Gy.[16,17,22] In many patients with advanced head and neck cancer treated with conventional 3D-radiation, the salivary glands will receive a considerable dose, which exceeds 45 Gy in the majority of cases. Although recent publications suggest that xerostomia may recover with elapsing time in some patients;[15] in most patients, the damage induced by radiation is irreversible. Therefore, these results underline the need to prevent the development of radiation-induced xerostomia.

It has been often assumed that xerostomia is closely related to other dimensions of QoL. However, most studies reporting on radiation-induced xerostomia and QoL have a descriptive character and they are often cross-sectional.[23,24,25] Bansal et al.[23] observed an increase in symptom score with increasing acute radiation morbidity, including xerostomia. This increase was associated with a deterioration in physical, emotional and social functioning and global QoL. However, in that study, the impact of xerostomia on QoL and related parameters was not reported. Ringash et al.[25] also studied the course of quality of life and radiation-induced xerostomia. They observed a recovery of QoL back to baseline after radiotherapy despite persistent xerostomia. In addition, Fisher et al.[24] observed no effect of the prevention of radiation-induced xerostomia by pilocarpine on QoL. However, in all these studies, follow up was restricted to 1-6 months after radiotherapy, limiting conclusions with regard to long-term effects. Also the low compliance,[24] the small number of patients,[23] the use of different questionnaires compared to our study[24,25] and the inclusion of post-operative patients[25] may explain why no association of xerostomia with QoL was seen in the aforementioned studies.

Another difficulty in comparing studies in which xerostomia has been evaluated, results from the heterogeneity regarding the methods of evaluation. Most grading systems of xerostomia are based on functional disabilities as salivary flow,[12,13,14] but also xerostomia-specific questionnaires are used.[16,26,27] A lack of concordance between objective endpoints of xerostomia like salivary flow and xerostomia-related questionnaires

assessing patient-rated xerostomia has been reported.[16,28,29,30] Observer-based (physician rated) toxicity scoring systems do not have to correlate with subjective endpoints as experienced by patients. Recently, Jensen et al.[31] reported about the relation between the observer-based toxicity scoring DAHANCA system and subjective endpoints measured with the EORTC QLQ-C30 and H&N35 questionnaire as assessed by patients. In this study the DAHANCA scoring system was insensitive and non-specific with regard to subjective endpoints. Another problem with the assessment of xerostomia is the potential lack of sensitivity for most tests, possibly explaining negative results. Recently, Eisbruch et al.[16] described a validated xerostomia questionnaire containing 8 questions on xerostomia, rated on an 11-point Likert scale. Such validated questionnaires, addressing different aspects of xerostomia and xerostomia-related symptoms may possibly enable to detect more subtle changes.

In the present study, additional analyses were performed to examine the impact of pre-treatment and treatment characteristics on the impact of xerostomia and QoL. A significant interaction term was present for age and sex with RTOG-xerostomia. In female patients, a more pronounced effect of xerostomia was observed on different QoL-dimensions. In some other studies, worse QoL among female patients after cancer treatment were observed[32,33] however, no data is available regarding the impact of radiation-induced xerostomia on QoL as performed in the present study. A possible explanation for the higher impact of xerostomia on QoL-related domains in female patients is that in general, women experience more insomnia than men.[34] This risk may be further increased by radiation-induced xerostomia, leading to a higher impact on fatigue resulting in a more negative effect on cognitive, social and role functioning and global QoL. Furthermore, we observed that RTOG-xerostomia had a higher impact on physical and social functioning and insomnia among younger patients. More specifically, in these domains younger patients seemed to suffer more from the same grade of xerostomia compared to elderly patients. A possible explanation could be that younger patients have a more active social life and that xerostomia-related side effects have therefore a greater impact on daily functioning, which is supported by the higher impact on social functioning in younger patients. As a consequence, more active patients will have a higher probability of a disturbed social and physical functioning.

In conclusion, radiation-induced xerostomia is not only the most frequently reported side effect in head and neck cancer patients after radia-

tion,[6,35] but also has a significant impact on different more general dimensions of QoL. This effect increases with time and is more pronounced in female and younger patients. Therefore, prevention of radiation-induced xerostomia, e.g. by IMRT, may have a significant impact on long term quality of life.

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Chapter 3

Does radiation dose to the salivary glands and oral cavity predict patient-rated xerostomia and sticky saliva in head and neck cancer patients treated with curative radiotherapy?

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Abstract

Purpose: to investigate the association between the mean salivary gland and oral cavity dose, with patient-rated moderate and severe xerostomia and sticky saliva.

Material and methods: 157 patients treated with bilateral irradiation for head and neck cancer were included. The parotid and submandibular glands and the oral cavity were delineated on plannings-CT scans. At baseline and 6 and 12 months self-reported xerostomia and sticky saliva were assessed using the EORTC QLQ-H&N35 questionnaire.

Results: At six months a significant association between the mean parotid (MD_{par}) and mean submandibular dose (MD_{subm}) and xerostomia was observed (OR- MD_{par}: 1.17; p=0.002 and OR- MD_{subm}: 1.08; p= 0.02). Between MD_{par} and MD_{subm} a significant interaction term was present. No significant association was found with the oral cavity dose. Xerostomia was reversible depending on MD_{par} and MD_{subm}.

Considering sticky saliva, a significant association was found at 6 and 12 months with MD_{subm} (OR: 1.03; p<0.001). The P50 for sticky saliva increased with elapsing time.

Conclusions: both MD_{par} and MD_{subm} influence the risk of xerostomia in irradiated patients at six months. This probability as a function of the mean parotid dose significantly depended on the mean dose in the submandibular glands. Sticky saliva mainly depends on MD_{subm}.

Introduction

Xerostomia is the most prevalent late side effect as reported by patients with head and neck cancer treated with radiation therapy.[1,2] It includes the objective reduction in the salivary output and changes in its composition and sensation of dry mouth. Changes in composition may lead to complaints of sticky saliva.

Although it is clear that radiation to the head and neck area causes xerostomia, the exact relation between radiation dose to the relevant anatomic structures and patient-rated xerostomia is still unclear. Studies of dose-volume/response relationships in the major salivary glands have primarily focused on the parotid glands. In earlier studies, it was reported that the parotid salivary flow was reduced to 60-70% of baseline following 10-14 Gy,[3,4] and was undetectable after 40-66 Gy.[3,5,6] Adequate analysis of this relationship with xerostomia requires 3D-information derived from planning-CT scans with an accurate delineation of the organs at risk and analysis of the exact dose in these organs by dose-volume histograms (DVH). More recently, a number of authors[7,8,9] reported on the association between salivary flow and irradiation of parotid glands using 3D-information derived from DVH's. In these studies, threshold doses for stimulated saliva production were found varying from 25 to 43 Gy. The common finding in these studies was that the probability of a significant reduction in stimulated salivary flow was best predicted by the mean parotid dose.

Most grading systems of xerostomia and endpoints in studies assessing dry mouth are based on functional disabilities.[10,11,12] However, in clinical practice, xerostomia is primarily a quality of life issue. In some studies, a lack of concordance between objective endpoints of xerostomia and xerostomia-related questionnaires assessing patient-rated xerostomia has been reported.[13,14,15] Therefore, information about the relationship between the dose distribution in the parotid glands and the risk of patient-rated xerostomia is scarce.

The aim of this prospective study was to investigate the association between the mean parotid dose (MD_{par}) with the incidence of self-reported xerostomia and sticky saliva among patients treated with irradiation for head and neck cancer. The hypothesis to be tested was that a high MD_{par} was associated with worse patient-rated xerostomia and sticky saliva. Secondly, the influence of the dose distribution in the submandibular glands and the minor salivary glands lining the oral cavity on patient-rated xerostomia and sticky saliva was investigated.

Material and methods

Patients

Patients eligible for this study were those with stage I-IVB[16] squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, nasopharynx and/or larynx. All patients were treated with primary or postoperative radiotherapy with curative intent, with a minimal life expectancy of 12 months. A good understanding of Dutch language was required to be able to complete the questionnaire. Excluded were those with distant metastases (M1), previously irradiated patients, patients treated in combination with induction or concurrent chemotherapy and patients with a tumour originating in the salivary glands. Patients who were treated with unilateral irradiation were not eligible. The study was approved by the Medical Ethical Committee of the VU University Medical Center. Informed consent was obtained for all patients. From august 1999 to august 2003, 156 patients met the eligibility criteria and completed the baseline questionnaire.

For the analysis of xerostomia, only patients with no or minimal xerostomia at baseline were included. The number of patients remaining for this analysis was 125. Similarly, for the analysis of sticky saliva, only those with no or minimal complaints at baseline were included. The number of patients remaining for this analysis was 129. The demographic and tumour characteristics of these two study populations are listed in Table 1.

Assessment of patient-rated xerostomia and sticky saliva

To assess xerostomia and sticky saliva, the EORTC QLQ-H&N35 was used.[17] This questionnaire contains 35 questions concerning treatment-related symptoms and symptoms frequently present in head and neck cancer patients. This questionnaire is organized into seven multi item scales and eleven single item scales, including xerostomia and sticky saliva. All scales are rated on a four-point Likert-scale. All sub-scales are linearly converted to a 0 to 100 scale. Higher scores represent a greater degree of symptoms.[18] The questionnaire was administered to the patients together with the EORTC QLQ-C30.The reliability and validity of both questionnaires have been confirmed in a number of international studies.[19,1,20] It has been translated for use among Dutch patients.

The questionnaire was administered before the start of treatment (baseline), and subsequently 6 weeks, 6 months and 12 months after

Table 1: Patients characteristics

	Patients eligible for xerostomia analysis (n=125)		Patients eligible for sticky saliva analysis (n=129)	
Variable	Number	%	Number	%
Sex				
Female	23	18%	26	(20%)
Male	102	82%	103	(80%)
Type of radiation				
Primary	95	76%	100	(78%)
Postoperative	30	24%	29	(22%)
T-classification				
T1-T2	103	82%	112	87%
T3-T4	22	18%	17	13%
N-classification				
N0	107	86%	118	91%
N+	18	14%	11	9%
Site				
Oral cavity	12	10%	13	10%
Oropharynx	17	14%	16	12%
Hypopharynx and larynx	91	73%	96	74%
Unknown primary	1	1%	1	1%
Other	4	3%	3	2%

completion of radiation. Patients were asked to participate during the first visit at the radiotherapy department. After informed consent, the questionnaire was distributed to the patients who were asked to fill in the questionnaire at the same time. During the regular follow up visits, the patients were asked by a research nurse to fill in the questionnaire before visiting the physician. When a patient did not comply with the planned visit, the questionnaire was send by mail. When the questionnaire was not returned within 4 days, the patient was phoned and asked to complete and return the questionnaire.

Radiotherapy

Radiotherapy was delivered using megavoltage equipment (6 MV linear accelerator). Generally, the initial target volume was irradiated

using two opposing lateral fields with an anterior field to cover the lower jugular and supraclavicular lymph node areas. The parotid and submandibular glands were outlined on planning CT-scans. To compose a 'distinct' organ for the minor salivary glands the oral cavity was outlined as has previously been described by Eisbruch et al.[14]

In case of primary radiotherapy for early glottic carcinoma, the initial field was irradiated with a fraction dose of 2.5 Gy (5 times/week) to a total dose of 60 Gy in 5 weeks. These patients were only irradiated at the primary site.

In case of primary radiotherapy of the more advanced cases that were considered not suitable for chemoradiation, an accelerated schedule with concomitant boost technique was used. These patients were generally treated with 6 fractions a week with a second fraction on Friday afternoon with a minimum interval of 6 hours, to a total dose of 70 Gy in 6 weeks. Most patients received bilateral elective irradiation of the neck nodes to a total dose of 46 Gy and a boost on the primary tumour and pathological lymph nodes to a total dose of 70 Gy.

In case of postoperative radiotherapy, conventional fractionation schedules were used. The target volume of the initial field encompassed the primary site plus a 2-centimetre margin and the entire surgical bed. In all cases, the neck nodes on both sides were also included in the initial target volume. The initial field was irradiated with a fraction dose of 2 Gy (5 times a week) to a total dose of 46 Gy. The boost dose varied from 56 Gy in case of negative surgical margins to 63.5 Gy in case of positive margins or lymph node metastasis with extranodal spread.

Statistics

Differences between mean scores between groups were tested with student's t-test, paired t-test or non-parametric tests when appropriate. Logistic regression analyses were performed to study the association between dose-volume parameters MD_{par}, the mean dose in the submandibular glands (MD_{subm}) and the mean dose in the oral cavity (MD_{oral}) and other baseline characteristics (sex, age, type of radiotherapy (primary of postoperative)) with the incidence of MS-XER and MS-SS at 6 and 12 months after completion of radiotherapy, respectively. Associations were expressed as odds ratio's (ORs) with their 95% confidence intervals (95% CI) per Gy increase in mean dose. An OR can be interpreted as a relative risk. The influence of possible confounding by other baseline characteristics was studied by adding these factors to the regression

models. Possible interaction (effect modification) by sex, age and type of radiotherapy was studied by adding the product terms to the model. Age was dichotomized at the median value (median age 66 years). In the analysis, female sex, age below the median and primary radiotherapy were used as reference. All analyses were performed by using SPSS for WINDOWS (version 11.0; SPSS Inc, Chicago).

Results

Compliance

Of the 125 patients available for analysis of patient-rated xerostomia, 111 out of 113 patients at risk (98%) returned the questionnaire at 6 months. The compliance at 12 months after radiotherapy was 94 out of 94 patients at risk (100%). Of the 129 patients available for analysis of patient-rated sticky saliva, 115 out of 119 patients at risk (97%) returned the questionnaire at 6 months. The compliance at 12 months after radiotherapy was 103 out of 109 patients at risk (94%).

Changes in patient-rated xerostomia

At baseline, the mean score of xerostomia was 11.7 (95% CI: 8.4-15.0) on a scale of 0-100, significantly increasing to 44.3 (95 % CI: 36.8-51.8) at 6 months and showing some recovery at 12 months to 37.9 (95 % CI: 30.8-45.1).

At 6 months, 23 out of 113 patients (20%) reported moderate xerostomia and 23 patients (20%) reported severe xerostomia, which brings the total percentage of patients with MS-XER at 41%. At 12 months, 23 out of 94 patients (25%) had moderate xerostomia, while 12 patients (13%) had severe xerostomia. The total percentage of patients with MS-XER was 38%.

Dose distribution and patient-rated xerostomia

The median MD_{par} was 24.2 Gy (Range: 0 - 68.9 Gy). The median MD_{subm} was 46.7 Gy (Range: 0 - 73.8 Gy) and the median MD_{oral} 9.1 Gy (Range: 0 - 67.3 Gy).

In the univariate logistic regression analysis, a significant association with MS-XER at 6 months was found with MD_{par}, MD_{subm}, MD_{oral} and the type of radiation (Table 2A). In the multivariate analysis, MD_{par} and MD_{subm} were the only two variables that were significantly associated

Table 2: Results of the univariate (A) and multivariate (B) logistic regression analysis with regard to moderate or severe xerostomia at 6 months.

A

Variable	Score	OR (95% CI)	p-value
Mean dose parotid glands	Continuous	1.09 (1.06 - 1.12)	< 0.001
Mean dose submandibular glands	Continuous	1.05 (1.03 - 1.08)	< 0.001
Mean dose oral cavity	Continuous	1.06 (1.03 - 1.08)	< 0.001
Age	0 = "18-66 years", 1= "> 66 years"	0.55 (0.26 - 1.19)	0.118
Sex	0= male, 1 = female	2.28 (0.87 - 5.95)	0.094
Type of radiation	0 = primary, 1 = postoperative	2.46 (1.01 - 6.02)	0.048

B

Variable	OR (95% CI)	p-value
Mean dose parotid glands (continuous) (MD_{par})	1.17 (1.06 - 1.29)	0.002
Mean dose submandibular glands (continuous) (MD_{subm})	1.08 (1.01 - 1.15)	0.019
Interaction term: MD_{par} x MD_{subm}	0.998 (0.996 - 1.000)	0.03

with MS-XER at 6 months (adjusted OR for MD_{par}: 1.17 (95% CI: 1.06-1.29); adjusted OR for MD_{subm}: 1.08 (95% CI: 1.01-1.15)). Moreover, a significant interaction term was present between MD_{par} and MD_{subm}, indicating that the effect of the MD_{par} depended on MD_{subm} (Table 2B).

A strong correlation was found between MD_{par} and MD_{oral} (Pearson correlation coefficient: 0.62; $p<0.001$) as well as between MD_{subm} and MD_{oral} (Pearson correlation coefficient: 0.71; $p<0.001$). In order to analyse the possible effect of MD_{oral}, an additional regression analysis was performed by adding the MD_{oral} to the model as outlined in Table 2B. No change was observed in the regression coefficients of the relationships between MD_{par}, MD_{subm} and MS-XER, indicating that MD_{oral} did not affect these relationships. In addition, the factors mentioned in Table 2B were added to a model with MD_{oral} as the only variable in which there was a strong and significant association between MD_{oral} and MS-XER, resulting in a dramatic change of the regression coefficient into a non-significant relationship between MD_{oral} and MS-XER.

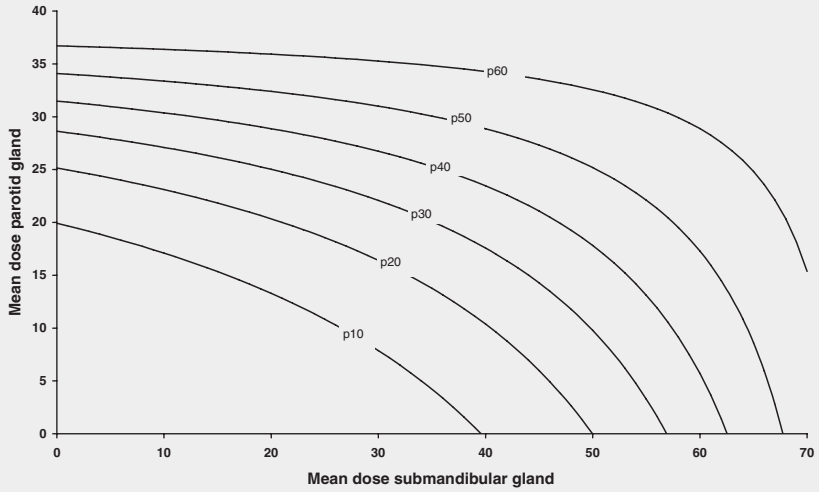


Figure 1: Probability curves for moderate or severe xerostomia at 6 months after radiation depending on the mean dose in the parotid glands and the mean dose in the submandibular glands. p10 denotes the 10%-probability of moderate or severe xerostomia at 6 months after radiotherapy.

At 12 months, in univariate analysis the same variables as found at 6 months were significantly associated with the incidence of MS-XER. In the multivariate logistic regression analysis, only MD_{par} was significantly associated with MS-XER (adjusted OR: 1.06 (95% CI: 1.01-1.12)) and, in

contrast with what was found at 6 months, no significant interaction terms were present.

In Figure 1, the probabilities of MS-XER at 6 months are shown as a function of the mean dose in the parotid glands and the mean dose in the submandibular glands. In Table 3, the p20- and p50-values of the mean dose of the parotid glands are shown as a function of the mean dose in the submandibular glands.

Table 3: The 20%- and 50%-probability mean parotid dose on moderate or severe xerostomia at 6 months after radiation as a function of the mean submandibular dose.

Mean dose submandibular gland	Mean dose parotid gland	
	p20	p50
0 Gy	25 Gy	34 Gy
10 Gy	23 Gy	33 Gy
20 Gy	20 Gy	32 Gy
30 Gy	16 Gy	31 Gy
40 Gy	10 Gy	29 Gy
50 Gy	0 Gy	25 Gy
60 Gy		17 Gy

As the MD_{par} and MD_{subm} were both significantly associated with patient-rated xerostomia, an additional analysis was performed to investigate the influence of MD_{par} and MD_{subm} on the mean score of xerostomia over time at 6 weeks, 6 months and 12 months (Figure 2). Patients were classified into four groups, depending on MD_{par} and MD_{subm}. The MD_{subm} was classified as low when it was $\leq$ 47 Gy (the median MD_{subm}) and high when it was > 47 Gy. The MD_{par} was also classified as low or high depending on whether it was $\leq$ median (24 Gy) or > median value. No significant changes over time were noted for those with a low parotid and low submandibular dose. A significant deterioration without a significant recovery of xerostomia was found among those with high MD_{par} and MD_{subm} and among those with a high dose in the submandibular glands and a low dose in the parotid glands. In case of a low dose in the submandibular glands and a high dose in the parotid glands, a significant worsening was noted after 6 weeks and 6

months, which, however, improved significantly after 12 months.

The relationship between dose and irradiated volume of the parotid glands was also analyzed by comparing the mean DVH for all patients stratified by the degree of xerostomia at 6 months (Figure 3A). The mean relative volumes at the different dose levels of the DVH's between patients with moderate and severe xerostomia at 6 months did not differ significantly. However, significant differences were present at dose levels up to 50 Gy between patients with no or a bit xerostomia at six months.

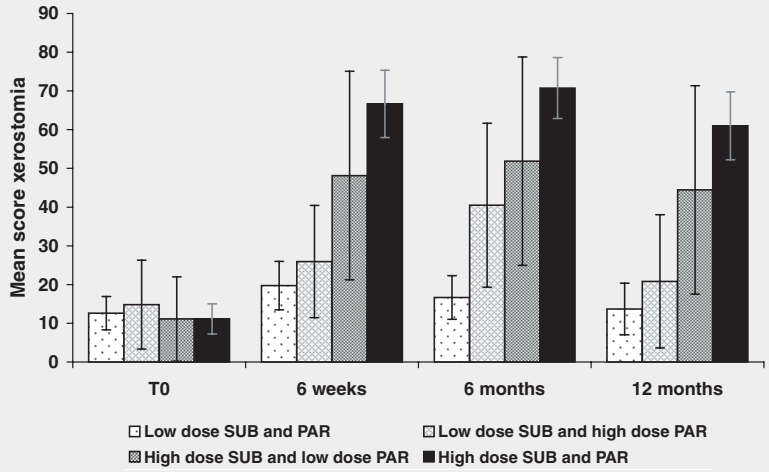
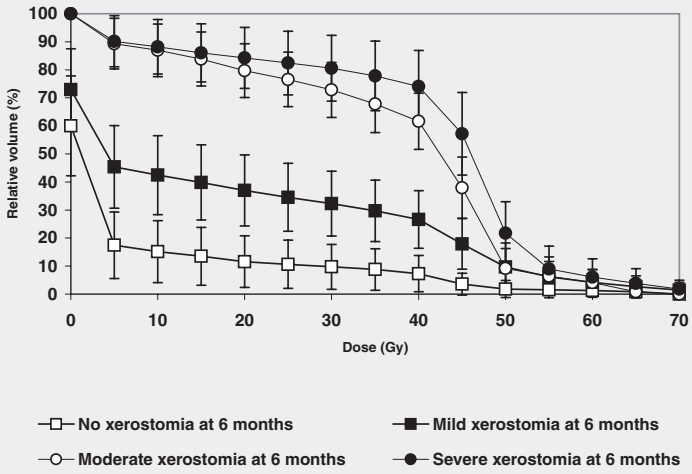


Figure 2: Mean scores for patient-rated xerostomia relative to the mean dose in the parotid glands and submandibular glands.
Low dose parotid glands = mean dose: 0-24 Gy; high dose parotid glands= mean dose > 24 Gy.
Low dose submandibular glands = mean dose: 0-47 Gy; high dose submandibular glands = mean dose > 47 Gy.
Abbreviations: PAR = parotid glands, SUB = submandibular glands.

Changes in patient-rated sticky saliva

At baseline, the mean score of sticky saliva was 7.0 (95% CI: 4.6–9.3) on a scale of 0-100, significantly increasing to 38.7 (95% CI: 32.1-45.3) at 6 months and showing some recovery at 12 months to 32.9 (95 % CI: 25.8-40.1). The same pattern was observed in the number of patients with MS-SS. At 6 months, 32 out of 122 patients (27%) reported moderate sticky saliva, while 15 patients (13%) reported severe sticky saliva, which brings the total percentage of patients with MS-SS at 40%. At 12 months, 24 out of 91 patients (26%) had moderate sticky saliva, while 7 patients (8%) had severe sticky saliva. The total percentage of patients with MS-SS was 34%.

A



B

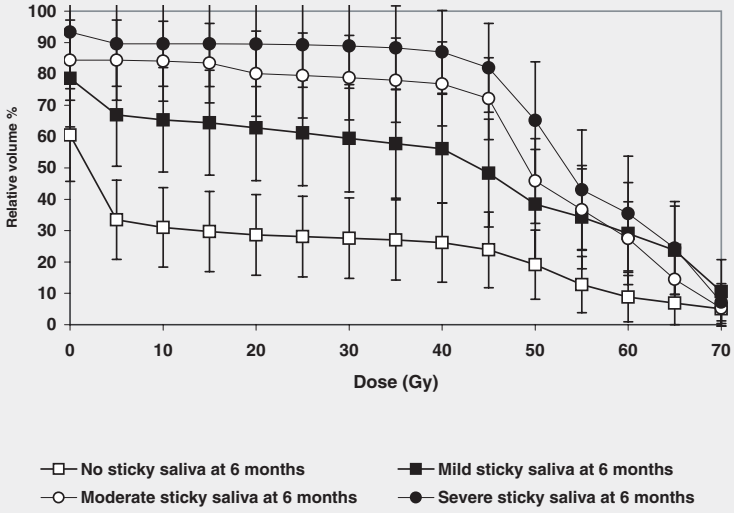


Figure 3: Mean DVH's of parotid glands stratified by patient-rated xerostomia (A) and Mean DVH's of submandibular glands stratified by patient-rated sticky saliva (B) at 6 months with 95%-confidence intervals.

Dose distribution and patient-rated sticky saliva

In the univariate analysis, a significant association was found between the MD_{par} and MD_{subm} with patient-rated sticky saliva at 6 months after completion of radiotherapy. No significant associations were found between the other variables and sticky saliva (Table 4).

Table 4: Results of the univariate logistic regression analysis with regard to moderate or severe sticky saliva at 6 months

Variable	OR	(95% CI)	p-value
Mean dose parotid glands (continuous)	1.04	(1.02 - 1.06)	< 0.001
Mean dose submandibular glands (continuous)	1.03	(1.02 - 1.05)	< 0.001
Mean dose oral cavity (continuous)	1.01	(0.99 - 1.03)	0.159
Age (0-66 versus > 66 years)	1.07	(0.51- 2.24)	0.851
Sex (male versus female)	1.69	(0.68 - 4.16)	0.257
Type of radiation (primary versus postoperative)	0.87	(0.38 - 2.27)	0.872

In the multivariate logistic regression analysis, MD_{subm} was the only factor significantly associated with patient-rated sticky saliva at 6 months (adjusted OR: 1.03 (95% CI: 1.02-1.05)). Similar results were found after 12 months (adjusted OR: 1.05 (95% CI: 1.02-1.07)). No significant interaction terms were found. As shown in Figure 4, the p50 for MS-SS increased with time after irradiation from 48 Gy at 6 months to 59 Gy at 12 months.

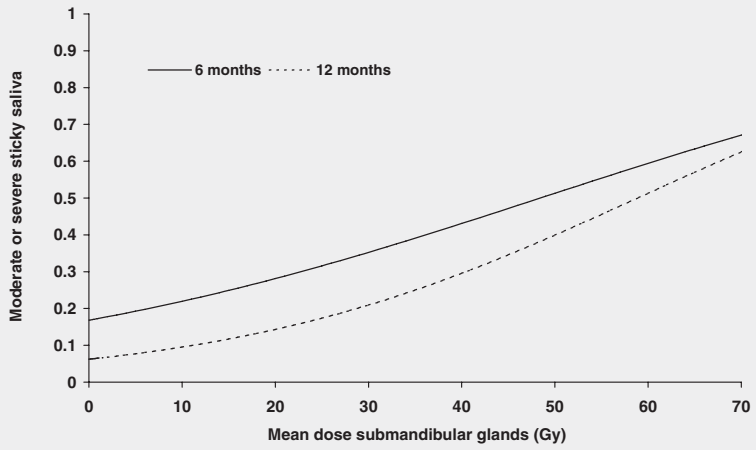


Figure 4: Probability of moderate or severe sticky saliva relative to the mean dose in the submandibular glands based on the multivariate logistic regression analysis.

The relationship between dose and irradiated volume of the submandibular glands was also analyzed by comparing the mean DVH for all patients stratified by the degree of sticky saliva at 6 months (Figure 3B). In general, a gradual increase was observed of the mean DVH's of patients with no, mild, moderate or severe sticky saliva at six months after completion of radiotherapy.

Discussion

Xerostomia is an important symptom after radiotherapy in the head and neck area affecting daily life.[2] Many studies have been published discussing the role of the dose in the parotid glands in radiation-induced xerostomia.[4,5,6,7,8,9,21,22,23,24]

The results of our study show that both the MD_{par} and MD_{subm} are the most important predictive factors for patient-rated xerostomia. Moreover, the probability of developing MS-XER as a function of MD_{par} dose 6 months after completion of radiation significantly increased with a higher MD_{subm}. This was illustrated by the increasing steepness of the probability curves with increasing doses in the submandibular glands (Figure 1). The results of this study clearly indicate that the prediction of patient-rated xerostomia is quite complex and does not only depend on the dose in the parotid glands. Moreover, the analysis of the longitudinal data up to 12 months after radiation shows that patient-rated xerostomia is partially reversible, depending on the dose in both the parotid and submandibular glands.

Most studies that investigated radiation-induced xerostomia focused on the physiological function of the parotid gland by measuring the salivary output[7,8,9] or by salivary gland scintigraphy.[25,26,15,27,28] In these studies, different threshold doses were found for the different endpoints. After introduction of CT-based planning, more precise dose-volume information became available. Maes et al. observed that keeping the $MD_{par} \leq 20$ Gy led to a good chance (≥70%) of preserving parotid function as measured by scintigraphy.[15] A correlation between the excretion function of the parotid glands and the subjective xerostomia scores as measured by a visual analogue scale and LENT/SOMA could not be demonstrated. Roesink et al. studied the relation between irradiated parotid gland volume and salivary output[9] or scintigraphy.[27] A mean dose (TD_{50}) for developing xerostomia at 12 months was reported depending on the endpoint used: 39 Gy for a 75% reduction of pretreatment stimulated salivary flow; 43 Gy for a decrease of parotid function to ≤ 45% of the

pretreatment value as measured by scintigraphy. Eisbruch et al.[7] observed a mean dose (TD_{50}) for developing xerostomia at 12 months of 26 Gy for a 75%-reduction of pretreatment stimulated salivary flow.

In two of the aforementioned studies, the role of partial volume irradiation has been evaluated, revealing a high correlation between partial volume threshold doses and mean volume threshold dose.[7,9] This suggests that assessing the mean volume dose is sufficient in predicting the chance of developing xerostomia.

Also questionnaires are used to investigate radiation-induced xerostomia.[14,29,30,31,32] Amosson et al.[30] reported on the relation between dosimetric parameters in radiotherapy and patient-rated xerostomia in patients treated with IMRT. In this study, several questions from a xerostomia-questionnaire were used as an endpoint. For each question, a different MD_{par} was observed. Therefore, no value for the relation between xerostomia in general and MD_{par} could be estimated. A relation between the stimulated whole saliva production, health related quality of life and MD_{par} at twelve months after therapy was observed in the study of Parliament,[32] though no TD_{50} was stated. They found no influence of surgical removal of the submandibular glands or irradiation of these glands to a high (>58 Gy) dose on unstimulated whole salivary flow. On the other hand, Eisbruch[14] reported a clear relationship between subjective xerostomia complaints and the dose in the submandibular glands. However, no TD_{50} for the dose in the submandibular glands was described, as there was no single endpoint for xerostomia. In contrast to our results, in this latter study also MD_{oral} was a significant predictor of patient-rated xerostomia. In order to investigate the possible role of MD_{oral}, an additional regression analysis was performed. No change was observed in the regression coefficients of the relationships between MD_{par}, MD_{subm} and MS-XER, indicating that MD_{oral} did not affect these relationships. In contrast, a dramatic change of the regression coefficient into a non-significant relationship between MD_{oral} and MS-XER, when MD_{par}, MD_{subm} were entered in a model with MD_{oral} as the only predictive factor. The combination of these results suggest that the association between the mean oral cavity dose and the probability on moderate or severe xerostomia as observed in the univariate regression analysis is mainly determined by the strong correlation of the mean oral cavity dose with the dose in the salivary glands and not by the dose distribution in the oral cavity itself. The difference regarding the role of the oral cavity dose between our findings and that of others may originate

in the different treatment techniques used in their study (also IMRT and unilateral irradiation). As far as we know our study is the first reporting on the quantitative relation of radiation dose and patient-rated xerostomia in head and neck cancer patients treated with conformal radiotherapy.

Besides xerostomia, sticky saliva is a frequently reported side effect of radiation, which is irreversible in a considerable proportion of patients. In this study, the MD_{subm} was the only significant radiation parameter significantly associated with sticky saliva. Similar to what was found for patient-rated xerostomia, the results indicate that there is some recovery of sticky saliva over time. The TD_{50} for MS-SS at 6 months was 49 Gy, which increased to 59 Gy at 12 months. Interestingly, for the risk of developing patient-rated sticky saliva, the only factor of interest was the MD_{subm}. The difference with the risk of developing patient-rated xerostomia may originate in the difference in composition of saliva produced.

Nowadays, parotid sparing is performed by optimizing radiation techniques using CT-based treatment planning and IMRT.[7,33] With most IMRT techniques, the dose in the parotid glands can be reduced at the cost of a higher dose in the oral cavity[34,35] and the question arises whether and to what extent this may counterbalance the beneficial effect of sparing the parotid glands. However, the results of the present study showed that the dose in the oral cavity did not affect the probability of patient-rated xerostomia and had no effect on the association between the MD_{par} and MD_{subm} and patient-rated xerostomia (no confounding and no effect modulation).

In conclusion, the risk of developing patient-rated MS-XER in irradiated patients is influenced by both the MD_{par} and MD_{subm}. This probability as a function of MD_{par} significantly increased with a higher MD_{subm}. Patient-rated sticky saliva mainly depends on MD_{subm} and shows some recovery over time.

Abbreviations

MS-XER is moderate and severe Xerostomia.
MS-SS is moderate and severe sticky saliva.

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Chapter 4

Unilateral versus bilateral irradiation in squamous cell head and neck cancer in relation to patient-rated xerostomia and sticky saliva

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Abstract

Background and purpose: to investigate the association between radiation technique with patient-rated moderate and severe xerostomia and sticky saliva.

Material and methods: 150 patients treated with bilateral or unilateral irradiation for head and neck cancer were included. The salivary glands and the oral cavity were delineated on plannings-CT scans. Xerostomia and sticky saliva were assessed using the EORTC QLQ-H&N35 questionnaire at baseline and 6 and 12 months.

Results: At 6 months a significant association between radiation technique and the mean parotid dose (MD_{parb}) and xerostomia was observed (Odds-ratio (OR)-technique: 2.55; p=0.04 and OR-MD_{parb}: 1.04; p= 0.009). Considering the individual salivary glands, only the mean dose in the contralateral parotid gland (MD_{parcl}) is associated with xerostomia (OR: 1.04; p<0.0001). Moreover, the threshold dose for a 50% probability (P50) on xerostomia increased from 21 Gy with bilateral to 44 Gy for unilateral irradiation.

Conclusions: Both technique and MD_{parb} influence the risk of xerostomia in irradiated patients. Of all individual salivary glands, only MD_{parcl} is of most importance for xerostomia. The shift in the P50 observed for xerostomia suggest that sparing of the contralateral parotid gland is compensated by hyperfunction of the contralateral parotid gland.

Introduction

Irradiation of patients with head and neck cancer often includes irradiation of the salivary glands. This may result in xerostomia, the most prevalent late side effect as reported by patients[1,2] and physicians.[3] It includes the objective reduction in saliva excretion by the salivary glands as well as patient-reported sensation of dry mouth. Changes in saliva composition may lead to complaints of sticky saliva. A reduced salivary output may lead to numerous side effects as saliva plays an important role in taste, mastication, digestion, swallowing and speech. Therefore, reduced salivary output may also have an impact on the more general dimensions of quality of life (QOL).

Although it is clear that radiation to the head and neck area causes xerostomia, the exact relation between radiation dose to the relevant anatomic structures and patient-rated xerostomia remains to be clarified. Recently, 3D-information was used in studies investigating the relationship between dose-volume parameters and xerostomia, using detailed information on the dose distribution in the salivary glands.[4,5,6,7,8] In these studies, threshold doses for stimulated saliva production were found varying from 22.5 to 43 Gy. The common finding was that the probability of a significant reduction in stimulated salivary flow mainly depended on the mean parotid dose.

Most studies concerning radiation and xerostomia involve patients treated with bilateral irradiation.[4,5,6,9,10,11] However, in some patients, e.g. in those with T1 or T2 tonsillar carcinoma, radiation can be limited to the ipsilateral neck, without compromising locoregional control.[10,12,11] The question arises whether the relationship between the mean dose in the parotid glands and xerostomia is similar among patients treated with unilateral irradiation as compared to patients treated with bilateral irradiation, in particular with regard to patient-rated xerostomia and other complaints, including sticky saliva.

Therefore, the aim of this prospective study was to investigate the association between the type of radiation technique (unilateral versus bilateral) with self-reported xerostomia and sticky saliva among patients treated with irradiation for head and neck cancer. The hypothesis to be tested was that bilateral irradiation of the head and neck area was associated with worse patient-rated xerostomia and sticky saliva. Secondly, the influence of the dose distribution in the parotid glands, submandibular glands and the minor salivary glands lining the oral cavity on patient-rated xerostomia and sticky saliva was investigated.

Material and methods

Patients

Patients eligible for this study were those with stage I-IVB[13] squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, paranasal sinus, nasopharynx, larynx, or an unknown primary tumor with lymph node metastases in the head and neck area. In all patients, unilateral or bilateral irradiation of the lymphnode regions in the neck was indicated. Patients treated with radiation only on the primary site were excluded (e.g. T1N0 laryngeal carcinoma). All patients, with a minimal life expectancy of 12 months were treated with primary or postoperative radiotherapy with curative intent. A good understanding of Dutch language was required to be able to complete the questionnaire. Patients with distant metastases (M1), previously irradiated patients, and/or patients treated in combination with induction or concurrent chemotherapy were excluded. Informed consent was obtained for all patients. The study was approved by the ethical committee of the VU University Medical Center. From August 1999 to August 2003, 150 patients met the eligibility criteria and completed the baseline questionnaire.

Assessment of patient-rated xerostomia and sticky saliva

Details on assessment of xerostomia and sticky saliva have been reported before.[14] In summary, the questionnaire was administered before the start of treatment (baseline), and subsequently at 6 weeks and with 6 months intervals from 6 months till 24 months after completion of radiation.

For the analysis of xerostomia, only patients with no or minimal xerostomia before radiotherapy were included. The number of patients remaining for this analysis was 117. Similarly, for the analysis of sticky saliva, only those with no or minimal complaints at baseline were included. The number of patients remaining for this analysis was 126.

The demographic, tumor and treatment characteristics of the study population are listed in Table 1.

Radiotherapy

Details on radiation therapy have been reported previously.[14] In summary, all patients were treated with 6-megavolt equipment using isocentre techniques after 3D-planning. No patients were treated with intensity-modulated radiotherapy (IMRT). Generally, the initial target volume

Table 1: Patients characteristics

Variable	Ipsilateral (n=55)		Bilateral (n=95)		P-value
	Number	%	Number	%	
Sex					0.03
Female	26	47%	28	30%	
Male	29	53%	67	70%	
Age					ns
18-65	27	49%	49	52%	
>65	28	51%	46	48%	
Type of radiation					< 0.001
Primary	16	29%	59	62%	
Postoperative	39	71%	32	34%	
T-classification					< 0.001
T1-T2	36	65%	64	67%	
T3-T4	19	35%	30	32%	
N-classification					p=0.06
N0	32	58%	70	74%	
N+	23	42%	25	26%	
Site					< 0.001
Oral cavity	33	60%	12	13%	
Mobile tongue	11	20%	3	3%	
Floor of mouth	3	6%	6	6%	
Alveolar process	7	12%	1	1%	
Cheek mucosa	6	11%	0	0%	
Miscellanuous	6	11%	4	4%	
Oropharynx	11	20%	27	28%	
Base of tongue	1	2%	8	8%	
Tonsillar fossa	9	16%	16	17%	
Miscellanuous	1	2%	3	3%	
Hypopharynx and larynx	0	0%	55	57%	
Supraglottic larynx	0	0%	23	23%	
Glottic larynx	0	0%	30	30%	
Miscellanuous	0	0%	2	2%	
Unknown primary	5	9%	1	1%	
Other	6	11%	0	0%	
Submandibular gland					p=0.02
In situ	32	58%	37	39%	
Removed during surgery	23	42%	58	62%	

was irradiated using two opposing lateral fields with an anterior field to cover the lower jugular and supraclavicular lymph node areas. All patients treated with primary radiotherapy received 46 Gy on elective treated areas. Regions containing macroscopic tumour received 70 Gy.

In case of postoperative radiotherapy, conventional fractionation schedules were used. The target volume of the initial field encompassed the primary site plus a 2-centimetre margin and the entire surgical bed. The initial field was irradiated with a fraction dose of 2 Gy (5 times a week) to a total dose of 46 Gy. The boost dose varied from 56 Gy in case of negative surgical margins to 63.5 Gy in case of lymph node metastasis with extra nodal spread or positive margins. In general, irradiation of the contralateral neck nodes was omitted when the expected risk of subclinical disease was below 15%. Patients were treated with unilateral radiation in case of well-lateralized tumors, i.e. at least 1 cm from the midline and not invading the soft palate and/or base of tongue.[11] In these cases, only the ipsilateral neck was included in the CTV. To correct for set up errors, an extra margin of 0.5 centimeter was taken for the planning target volume (PTV). In general, two opposing anterior-posterior and posterior-anterior fields were used for the cranial part of the PTV and an additional single anterior field to cover the ipsilateral low jugular and supraclavicular nodal regions. In some cases, for the cranial part an additional low weighted lateral field was used in order to spare a larger amount of the anterior part of the oral cavity.

The parotid and submandibular glands were outlined on planning CT-scans. To compose a 'distinct' organ for the minor salivary glands the oral cavity was outlined as has previously been described by Eisbruch et al.[15]

Statistics

Differences between mean scores between groups were tested with student's t-test, paired t-test or non-parametric tests when appropriate. Logistic regression analyses were performed to study the association between radiation technique (unilateral versus bilateral), dose-volume parameters (mean dose both parotid glands (MD_{parb}), mean dose ipsilateral (MD_{paril}) and contralateral parotid gland (MD_{parcl}), mean dose both submandibular glands (MD_{subb}), mean dose ipsilateral (MD_{subil}), and contralateral submandibular gland (MD_{subcl}), and mean dose oral cavity (MD_{oral}), and other baseline characteristics (sex, age, type of radiotherapy (primary or postoperative) and surgery to the neck (yes or no) with the

incidence of moderate or severe xerostomia and moderate or severe sticky saliva at 6 months after completion of radiotherapy. Associations were expressed as odds ratio's (ORs) with their 95% confidence intervals (95% CI) per Gy increase in mean dose. An OR can be interpreted as a relative risk. The influence of possible confounding by other baseline characteristics was studied by adding these factors to the regression models. Possible interaction (effect modification) by sex, age and type of radiotherapy was studied by adding the product terms to the model. Age was dichotomized at the median value (median age 65 years). In the analysis, female sex, age below the median and primary radiotherapy were used as reference. All analyses were performed by using SPSS for WINDOWS (version 11.0; SPSS Inc, Chicago).

Results

Compliance

Of the 117 patients available for analysis of patient-rated xerostomia, 107 out of 111 patients at risk (96%) returned the questionnaire at 6 months. The compliance remained at this level during longer follow up: 97% at 12 months (94 out of 97 patients) and 97% at 24 months (66 out of 68 patients).

Similar compliance rates were observed for sticky saliva. Of the 126 patients available for analysis, 115 out of 119 patients at risk (95%) returned the questionnaire at 6 months after radiotherapy. The compliance was 97% at 12 months (98 out of 101 patients), and 97% at 24 months (67 out of 69 patients).

Changes in patient-rated xerostomia

At baseline, the mean score of xerostomia for all patients was 25.5 (95% CI: 20.4-30.6) on a scale of 0-100, significantly increasing to 57.5 (95% CI: 51.9-63.1) at 6 months and showing some recovery at 12 months to 51.3 (95% CI: 44.7-57.9).

Among patients treated with unilateral irradiation the mean score for xerostomia was 29.7 (95% CI: 20.9-38.5) on a scale of 0-100 at baseline, significantly increasing to 43.8 (95% CI: 35.0-52.6) at 6 months, showing recovery at 12 months to 38.9 (95% CI: 27.8-50.0) and returning to baseline level at 24 months (mean score 30.2 (95 % CI: 17.5-42.9)(Figure 1).

Among patients treated bilaterally, the mean score for xerostomia was

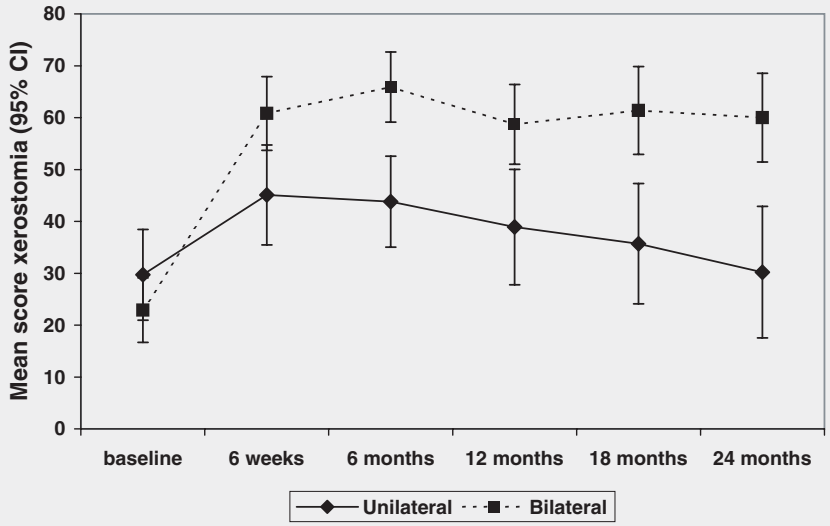

Figure 1. Mean score of patient-rated xerostomia after radiation according to type of radiotherapy (uni- versus bilateral).

22.9 (95% CI: 16.7-29.1) on a scale of 0-100 at baseline, significantly increasing to 65.9 (95% CI: 59.1-72.7) at 6 months and showing some recovery at 12 months to 58.7 (95% CI: 51.0-66.4). After 12 months no important changes were observed (Figure 1). At all time points, except at baseline (p=0.2), the mean score for xerostomia among patients treated with unilateral irradiation differed significantly from that among those treated with bilateral irradiation ($p \leq 0.01$).

Dose distribution and patient-rated xerostomia

To analyze the association between the type of radiation, the dose distributions in the organs at risk and patient-rated xerostomia, the mean doses in the oral cavity and the parotid and submandibular glands were used.

Among patients treated with unilateral irradiation, the values for the mean dose of the organs at risk were significantly lower compared to bilaterally treated patients, except for mean oral cavity dose (MD_{oral}) (Table 2).

In the univariate logistic regression analysis, a significant association between moderate or severe xerostomia at 6 months was found with MD_{parb}, MD_{parcl}, MD_{subb}, MD_{subcl}, and type of radiation (Table 3). In the multivariate analysis, in which MD_{subb}, MD_{parb} and type of radiation

Table 2. Mean dose in organs at risk for all patients included.

Variable	Ipsilateral (n=55)			Bilateral (n=95)			Total (n=150)			P-value
	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range	
Mean dose both parotid glands (continuous)	24.6	25.3	7.1 - 41.7	37.8	40.1	13.1 - 68.9	33.0	33.2	7.1 - 68.9	<0.001
Mean dose ipsilateral parotid gland (continuous)	45.4	48.4	14.7 - 68.8	39.2	39.5	10.0 - 70.9	41.5	42.4	10.0 - 70.9	0.03
Mean dose contralateral parotid gland (continuous)	5.9	3.1	0.40 - 34.7	36.7	39.4	11.5 - 68.2	25.4	30.3	0.40 - 68.2	<0.001
Mean dose both submandibular glands (continuous)	38.9	40.0	19.5 - 54.5	56.0	55.9	39.9 - 73.8	51.5	50.5	19.5 - 73.8	<0.001
Mean dose ipsilateral submandibular gland (continuous)	59.3	60.8	46.2 - 72.3	55.2	55.1	22.2 - 74.1	56.3	56.8	22.2 - 74.1	ns
Mean dose contralateral submandibular gland (continuous)	13.3	10.8	0.0 - 37.6	55.8	55.1	16.8 - 73.5	39.4	47.5	0.0 - 73.5	<0.001
Mean dose oral cavity (continuous)	24.4	30.2	4.0 - 53.0	26.4	17.4	3.0 - 67.0	25.6	21.3	3.0 - 67.0	n.s

Table 3 : Results of the univariate logistic regression analysis with regard to moderate or severe xerostomia at 6 months.

Variable	Abbreviation	OR	(95% CI)	P-value
Mean dose both parotid glands (continuous)	MD_{parb}	1.05	(1.02 - 1.09)	0.001
Mean dose ipsilateral parotid gland (continuous)	MD_{paril}	1.02	(0.99 - 1.04)	ns
Mean dose contralateral parotid gland (continuous)	MD_{parcl}	1.04	(1.02 - 1.07)	<0.001
Mean dose both submandibular glands (continuous)	MD_{subb}	1.02	(1.00 - 1.04)	0.02
Mean dose ipsilateral submandibular gland (continuous)	MD_{subil}	1.00	(0.99 - 1.01)	ns
Mean dose contralateral submandibular gland (continuous)	MD_{subcl}	1.03	(1.01 - 1.05)	0.002
Mean dose oral cavity	MD_{oral}	1.03	(0.98 - 1.02)	ns
Surgery to the submandibular gland (yes or no)		0.98	(0,45 - 2,1)	ns
Uni- vs bilateral irradiation		3.80	(1.60 - 8.70)	0.001

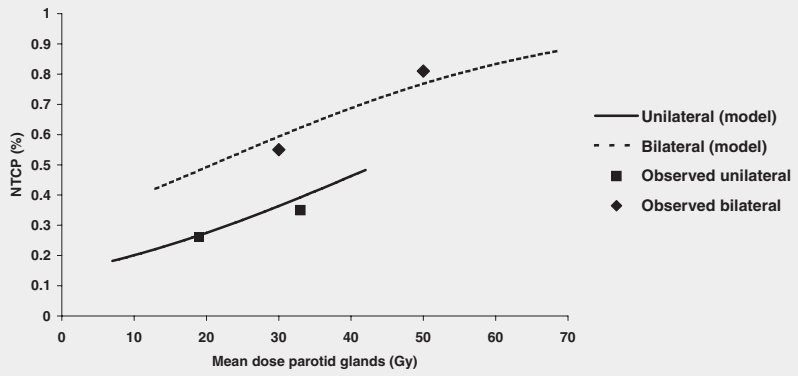

Figure 2: Association (observed versus model) between the mean dose in both parotid glands and the probability of moderate or severe xerostomia (EORTC QLQ-H&N35).

were entered as variables, only MD_{parb} and type of radiation were significantly associated with moderate or severe xerostomia at 6 months. The adjusted OR (after correction for confounders) for MD_{parb} was 1.04 (95% CI: 1.01-1.08) (p=0.009) and the adjusted OR for type of radiation was 2.55 (95% CI: 1.05-6.2) (p=0.04) (Table 4). In Figure 2, the probability of moderate or severe xerostomia at 6 months is shown as a function of the mean dose in the parotid glands, stratified by uni- versus bilateral irradiation.

As MD_{parb} and type of radiation were both significantly associated with patient-rated xerostomia, an additional analysis was performed to investigate the influence of the mean dose of the individual salivary glands on patient-rated xerostomia. The only variable in this second analysis significantly associated with moderate or severe xerostomia at 6 months was MD_{parcl} (adjusted OR for MD_{parcl}: 1.04 (95% CI: 1.02-1.07);

p<0.0001)(Table 4). No significant associations were found between the other variables (MD_{paril}, MD_{subb}, MD_{subil}, MD_{subcl}, MD_{oral} and surgery to the neck) and moderate or severe xerostomia.

Table 4 : Results of the multivariate logistic regression analysis with regard to moderate or severe xerostomia at 6 months.

Variable	OR	(95% CI)	P-value
Model 1 with MD_{parb} MD_{subb} and type of radiation			
Mean dose both parotid glands (continuous)	1.04	(1.01 - 1.08)	0.009
Uni- versus bilateral irradiation	2.55	(1.05 - 6.16)	0.04
Model 2 with MD_{paril}, MD_{parcl}, MD_{subcl}, MD_{subil}			
Mean dose contralateral parotid gland (continuous)	1.04	(1.02 - 1.07)	<0.001

NOTE: Only significant factors are mentioned
* Model 1: Included MD_{parb} MD_{subb} and type of radiation
** Model 2: included MD_{paril}, MD_{parcl}, MD_{subcl}, MD_{subil} and MD_{oral}

Changes in patient-rated sticky saliva

At baseline, the mean score of sticky saliva for all patients was 18.8 (95% CI: 14.3-23.3) on a 0-100 scale, significantly increasing to 50.2 (95% CI: 43.9-56.5) at 6 weeks and showing some recovery at 6 months to 44.2 (95% CI: 37.9-50.5).

For patients treated with unilateral irradiation, the mean score for sticky saliva was 17.6 (95% CI: 10.2-25.0), significantly increasing to 33.3 (95 % CI: 24.0-42.6) at 6 weeks and showing a substantial recovery at 6 months to 23.7 (95 % CI: 15.2-32.2) (Figure 3.)

For patients treated bilaterally, the mean score for sticky saliva was 19.6 (95% CI: 13.9-25.3) at baseline, significantly increasing to 60.3 (95% CI: 52.6-68.0) at 6 weeks and showing some recovery at 6 months to 57.0 (95 % CI: 49.5-64.5) (Figure 3).

At all time points, except at baseline, the mean score for sticky saliva among patients treated with unilateral irradiation differed significantly from that among those treated with bilateral irradiation ($p \leq 0.01$).

Dose distribution and patient-rated sticky saliva

In the univariate analysis, a significant association was found between the MD_{parb}, MD_{parcl}, MD_{subcl}, MD_{subb} surgery to the neck and type of irradiation with patient-rated sticky saliva at 6 months after completion of radiotherapy. No significant associations were found between MD_{paril}, MD_{subil} and MD_{oral} with sticky saliva (Table 5).

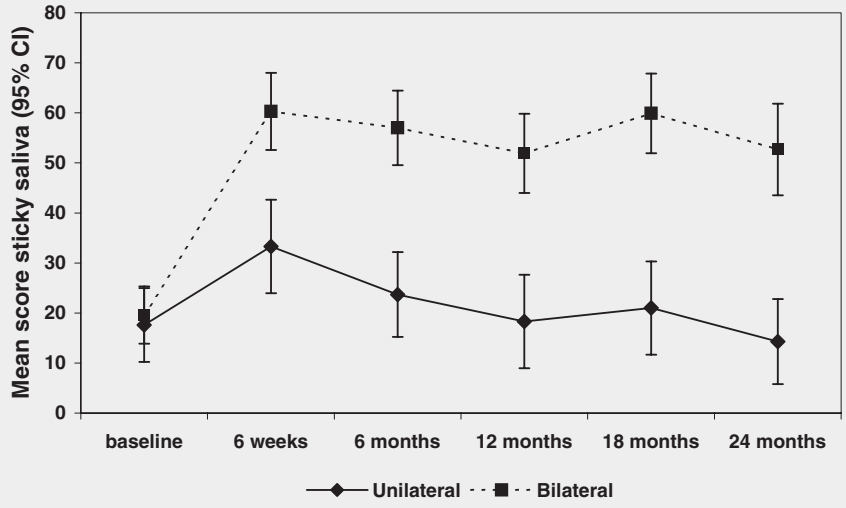

Figure 3. Mean score of patient-rated sticky saliva after radiation according to type of radiotherapy (uni- versus bilateral).

In the multivariate logistic regression model in which type of radiation, MD_{parb}, and MD_{subb} were entered, type of radiation was the only factor significantly associated with patient-rated sticky saliva at 6 months (adjusted OR: 7.01 (95% CI: 2.91-17.02) p<0.0001)). In addition, a second multivariate analysis was performed in which each individual salivary gland and surgery to the neck was entered in the model. In this second model, the only variable that was significantly associated with sticky saliva was MD_{subcl} (adjusted OR for MD_{subcl}: 1.03 (95% CI: 1.02-1.06), p<0.0001).

Table 5 : Results of the univariate logistic regression analysis with regard to moderate or severe sticky saliva at 6 months.

Variable	Abbreviation	OR	(95% CI)	P-value
Mean dose both parotid glands (continuous)	MD_{parb}	1.02	(1.01 - 1.05)	0.07
Mean dose ipsilateral parotid gland (continuous)	MD_{paril}	0.99	(0.97 - 1.01)	n.s.
Mean dose contralateral parotid gland (continuous)	MD_{parcl}	1.03	(1.01 - 1.06)	0.002
Mean dose both submandibular glands (continuous)	MD_{subb}	1.04	(1.01 - 1.06)	0.002
Mean dose ipsilateral submandibular gland (continuous)	MD_{subil}	1.01	(1.00 - 1.02)	n.s.
Mean dose contralateral submandibular gland (continuous)	MD_{subcl}	1.03	(1.01 - 1.05)	<0.001
Mean dose oral cavity	MD_{oral}	0.99	(0.98 - 1.01)	ns
Surgery to the submandibular gland (yes or no)		3.00	(1,4 - 6,4)	0.005
Uni- vs bilateral irradiation		7.00	(2.91-17.02)	<0.001

Discussion

This prospective cohort study was performed to assess the consequences of unilateral versus bilateral irradiation with regard to patient-rated xerostomia and sticky saliva. The results indicate that after completion of radiotherapy these complaints were more pronounced among patients treated with bilateral irradiation than among those treated with unilateral irradiation.

First, these differences were reflected in the response rates for xerostomia and sticky saliva at 6 months, which were significantly higher among bilaterally irradiated patients than among those treated with unilateral radiotherapy.

Second, after unilateral irradiation, both xerostomia and sticky saliva decreased to a level similar to the baseline level before radiation. This was not the case after bilateral irradiation, in which both xerostomia and sticky saliva remained more or less unchanged up to 24 months compared to 6 weeks after completion of treatment. Also Eisbruch et al.[15] observed a recovery of xerostomia in unilaterally irradiated patients which was accompanied with a compensatory overproduction of saliva in the contralateral parotid and submandibular gland at 12 -24 months. Furthermore, in rats, an enhanced proliferation of acinar cells was found in the remaining submandibular gland after surgical removal of one submandibular gland.[16] Therefore, it is suggested that the spared salivary gland compensates for the loss of function thereby improving xerostomia. This is supported by the findings of the present study in which the mean dose in the contralateral parotid gland was the most important prognostic factor for patient-rated xerostomia while the mean dose in the ipsilateral gland was of less importance. Furthermore, this was also supported by the striking finding that the probability of the development of moderate or severe xerostomia as a function of the mean parotid dose MD_{parb} was significantly different after unilateral and bilateral irradiation. This was reflected in an increase in the mean dose (TD_{50}) for moderate or severe xerostomia from 23 Gy for bilaterally treated patients to 45 Gy for unilaterally treated patients. These findings also indicate that the results obtained from studies in which patients are treated with bilateral irradiation, either with conventional techniques or IMRT, can not be translated to patients treated with unilateral irradiation.

In studies investigating the effect of treatment technique on the risk of developing radiation-induced xerostomia and sticky saliva, surgery to

the neck may be a potential confounder due to removal of a submandibular gland. In our study, a substantial group of patients in both arms had surgery to the neck. Also other studies on the impact of treatment technique report on postoperative irradiated patients, though the type of surgery is not stated.[15,17] When stratified for surgery, we observed no difference in baseline values for xerostomia (not shown). Furthermore, in the multivariate analysis surgery to the neck was not significant for the risk of patient-rated moderate or severe xerostomia and sticky saliva at six months. Therefore, in our study, surgery to the neck is not a confounding factor.

Nearly all studies concerning patient-rated xerostomia reported on the results obtained among patients treated with bilateral irradiation or IMRT.[18,4,15,19,20,21,22,23] One of the major problems in comparing the results of these studies is the heterogeneity regarding the endpoints used. The most frequently applied endpoints are salivary flow,[4,5,6,21] scintigraphy [19,24,25] and patient-rated xerostomia evaluated by questionnaires.[17,26] As a consequence, different TD_{50} values have been reported, varying from 25.8 Gy in case of reduced stimulated salivary flow to 25% of baseline[27] to 43 Gy in case of a decrease of parotid function to ≤ 45% of the pre-treatment value as measured by scintigraphy.[28]

One of the few studies describing xerostomia among patients treated with unilateral or bilateral radiotherapy is from Malouf et al.[17] In that study, the scores obtained by xerostomia questionnaires and salivary flow rates were better in patient groups treated with parotid-sparing techniques (unilateral or bilateral parotid sparing) compared to bilateral irradiation with standard 3-field technique. Moreover, the general QOL scales after parotid-sparing techniques were significantly better as compared to those reported by patients treated with standard 3-field techniques. However, in their study, the MD_{parcl} with parotid-sparing techniques was 3.8 Gy (unilateral irradiation) and 20.5 Gy for (IMRT), while it was 62.7 Gy for patients treated with standard 3-field techniques. Since the mean doses for bilaterally treated patients differed clearly from that in the present study, the results remain difficult to compare. However, from both studies it can be concluded that treatment technique has a major impact on the risk of developing patient-rated xerostomia.

Eisbruch et al.[15,5] reported on the results among patients treated with unilateral and bilateral irradiation. In these studies, response was defined as a decline in salivary gland flow to <25 % reference to baseline. The mean dose in the parotid glands,[5] the submandibular glands and the

oral cavity[15] were significant predictors of the risk of developing xerostomia. Though a TD_{50} for the parotid glands was observed of 26 Gy,[5] no TD_{50} for the submandibular glands or the oral cavity was reported. In a previous study in bilaterally treated patients, we showed that patient-rated xerostomia depended both on MD_{parb} and MD_{subb}.[14]

Concerning the minor salivary glands lining the oral cavity, conflicting results exists in bilaterally treated patients. Eisbruch et al.[15] found a significant association between mean dose in the oral cavity and patient-rated xerostomia. However, in our previous study we observed that the association between the mean dose in the oral cavity and the probability on moderate or severe xerostomia was most likely to be determined by the strong correlation of mean oral cavity dose with the dose in the salivary glands and not by the dose distribution in the oral cavity itself.[14] In the present study, mean oral cavity dose again was not a significant factor for patient-rated xerostomia in the multivariate analysis.

Besides xerostomia, sticky saliva is a frequently reported side effect of radiation, which is irreversible in a considerable proportion of patients. In this study, treatment technique and the mean dose in the contralateral submandibular gland were independent prognostic factors for sticky saliva. Similar to what was found for patient-rated xerostomia, a recovery of sticky saliva back to baseline was observed in unilaterally treated patients over time. The finding that sticky saliva is mainly determined by the submandibular rather than the parotid mean dose is supported by our previous findings.[14]

In conclusion, the development of radiation-induced patient-rated xerostomia and sticky saliva is significantly worse after bilateral compared to unilateral irradiation. After unilateral irradiation, patient-rated xerostomia and sticky saliva recovered to the baseline level. The probability on moderate or severe xerostomia is not only determined by the mean parotid dose, but also on the technique used.

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Chapter 5

Chemotherapy does not increase the probability of radiation-induced xerostomia in the treatment of squamous cell head and neck cancer

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Submitted

Abstract

Purpose: to investigate the association between type of treatment (radiotherapy with or without chemotherapy) and patient-rated moderate and severe xerostomia and sticky saliva.

Material and methods: 146 patients with head and neck cancer were included; 92 patients were treated with radiotherapy alone and 54 patients were treated with radiotherapy and chemotherapy. The parotid and submandibular glands were delineated on planning-CT scans. Self-reported xerostomia and sticky saliva were assessed using the EORTC QLQ-H&N35 questionnaire at baseline and at 6 and 12 months.

Results: In the univariate logistic regression analysis at 6 months only a significant association between the mean parotid dose (MD_{parb}) and xerostomia was observed. No significant relationships were found between treatment modality and xerostomia or with sticky saliva. In the multivariate logistic regression analysis only MD_{parb} remained significant and no interactions between the dose distributions in the salivary glands and treatment modality group were observed.

Conclusions: Only MD_{parb} influences the risk of xerostomia in patients treated with combined modality. We observed no increased risk of xerostomia due to the administration of chemotherapy.

Introduction

The majority of patients with head and neck cancer presents with locally advanced disease. Until recently, many of these patients were treated with a combination of surgery and postoperative radiotherapy.[1,2,3,4,5,6] However, in case of unresectable disease or in order to preserve organ function, an increasing number of patients are currently treated with combined modality treatment consisting of chemotherapy and radiotherapy.[7,8,9,10,11] Although concomitant chemoradiation has led to a significant improvement of the overall survival of approximately 8% after 5 years,[12] the prevalence of radiation-induced side effects (e.g. mucositis and dysphagia) are also increased as compared to radiotherapy alone.[7,13,14,15] Furthermore, chemotherapy by it self may lead to additional side effects such as nausea and vomiting, hair loss, renal toxicity, ototoxicity and bone marrow depression.[16,17,18]

The most frequently reported late side effect after radiation for head and neck cancer is xerostomia, which has also been reported as the most serious problem after radiation.[19,20,21] Xerostomia may result in numerous additional side effects as saliva plays an important role in taste, mastication, digestion, swallowing and speech. As a consequence, quality of life (QOL) is often impaired in head and neck cancer patients.[22]

The last decade, the relationship between radiotherapy and xerostomia has been studied extensively, showing a reduced parotid flow after inclusion of the major salivary glands in the radiation portals.[23,24,25,26,27,28,29,30,31] Recently, several studies using 3-D information have demonstrated threshold mean doses for stimulated saliva production varying from 22.5 to 43 Gy for the parotid gland.[23,24,25,27,32,33] However, little information is available on the risk of developing xerostomia among patients treated with combined modality, i.e. radiotherapy and chemotherapy. The question arises whether these patients have an increased risk of developing xerostomia, and more specifically, whether the relation between the mean dose in the salivary glands and xerostomia is different from patients treated with radiotherapy alone.

Therefore, the aim of this prospective study was to investigate the association between the type of treatment (radiotherapy with or without chemotherapy) with self-reported xerostomia and sticky saliva among patients with head and neck cancer. The hypothesis to be tested was that combined modality treatment was associated with worse patient-rated xerostomia and sticky saliva as compared to that observed after radiotherapy alone.

Patients and methods

Patients

Patients eligible for this study were those with stage I-IVB[34] squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, nasopharynx and/or larynx or with lymph node metastases in the head and neck area from an unknown primary tumour. All patients were treated with radiotherapy with or without chemotherapy and had a minimal life expectancy of 12 months. A good understanding of the Dutch language was required to be able to complete the questionnaire. All patients were treated with bilateral irradiation and the clinical target volume at least encompassed level II on both sides of the neck. Excluded were those with distant metastases (M1), previously irradiated patients, patients with a tumour originating in the salivary glands and patients that were treated with unilateral irradiation. The study was approved by the ethical committee of the VU University Medical Center. From January 2000 until May 2004, 146 patients met the eligibility criteria and were included in the study. Fifty-four patients were treated with chemotherapy and radiotherapy and this group was compared to 92 patients that were treated with radiotherapy alone.

Assessment of patient-rated xerostomia and sticky saliva

To assess patient-rated xerostomia and sticky saliva, patients were asked to fill in the EORTC QLQ-H&N35 questionnaire in addition to the EORTC QLQ-C30 questionnaire.[35,36,37] The questionnaire was administered before the start of treatment (baseline), and subsequently at 6 weeks and with 6 months intervals from 6 months till 24 months after completion of radiation. Patients were asked to participate in the study during the first visit at the radiotherapy department. After informed consent, the questionnaire was distributed to the patients who were asked to fill in the questionnaire at the same time. During the regular follow up visits, the patients were asked by a research nurse to fill in the questionnaire before visiting the physician.

The demographic and tumour characteristics of the study population are listed in Table 1. For the analysis of xerostomia, only patients with no or minimal xerostomia at baseline were included. The number of patients remaining for this analysis was 142. Similarly, for the analysis of sticky saliva, only those with no or minimal complaints of sticky saliva at baseline were included. The number of patients remaining for this

analysis was 141.

Table 1: Patients characteristics

	Chemotherapy (n=54)		No Chemotherapy (n= 92)		P-value
Variable	Number	%	Number	%	
Sex					
Female	15	28%	27	29%	n.s.
Male	39	72%	65	71%	
Age					
18-65	47	87%	47	51%	<0.001
>65	7	13%	45	49%	
T-classification					
T1-T2	8	15%	64	70%	<0.001
T3-T4	46	85%	28	30%	
N-classification					
N0	11	20%	68	74%	<0.001
N+	43	80%	24	26%	
Site					
Oral cavity	4	7%	11	12%	n.s.
Oropharynx	17	32%	27	29%	
Hypopharynx and larynx	28	52%	52	57%	
Other	5	9%	2	2%	

Radiotherapy

Details on radiation therapy have been reported in detail previously.[38] In summary, all patients were treated with 6 MV equipment using isocentre techniques after 3D-planning. All patients were treated with 3D-conformal radiotherapy (3D-CRT). Generally, the initial target volume was irradiated using two opposing lateral fields with an anterior field to cover the lower jugular and supraclavicular lymph node areas. All patients received 46 Gy on elective treated areas; regions containing macroscopic tumour received 70 Gy.

The parotid and submandibular glands were outlined on planning CT-scans. To compose a 'distinct' organ for the minor salivary glands the oral cavity was outlined as has previously been described by Eisbruch et al.[26]

Chemotherapy

Chemotherapy was given in 54 patients. Twenty patients received induction chemotherapy (four courses of cisplatinum 100 mg/m^2 + 5-FU 1000 mg/m^2 by continuous infusion every 3 weeks); 26 patients received concomitant chemoradiation (three courses of cisplatinum 100 mg/m^2 in weeks 1, 4 and 7) and 8 patients received alternating chemoradiation (four courses of cisplatinum 100 mg/m^2 + 5-FU 1000 mg/m^2 by continuous infusion in weeks 1, 4, 7 and 10, with radiotherapy in weeks 3 and 4, 5 and 6, and 8 and 9 to a total dose of 60 Gy). All patients with unresectable disease were treated with concomitant chemotherapy. Induction chemotherapy or alternating chemoradiation was only administered in patients with hypopharyngeal and laryngeal cancer.

Statistics

Differences between means were tested using a student-t test or non-parametric tests whenever appropriate.

Logistic regression analyses were performed to study the association between treatment (radiotherapy with chemotherapy versus radiotherapy alone), dose-volume parameters (mean dose both parotid glands (MD_{parb}), mean dose both submandibular glands (MD_{subb}), and mean dose oral cavity (MD_{oral})) with the incidence of moderate or severe xerostomia ($P_{xerostomia}$) and moderate or severe sticky saliva ($P_{sticky\ saliva}$) at 6 months after completion of radiotherapy. The 6 months time interval was chosen as the results of our previous studies showed that these complaints are most pronounced at 6 months and are highly predictive for the response rates at later time points. Associations were expressed as odds ratio's (ORs) with their 95% confidence intervals (95% CI) per 10 Gy increase in mean dose. An OR can be interpreted as a relative risk. The influence of the effect of chemotherapy was analyzed by adding interaction terms (effect modification) between dose-volume parameters and treatment modality to the model. All analyses were performed by using SPSS for WINDOWS (version 11.0; SPSS Inc, Chicago).

Results

Compliance

Of the 142 patients available for analysis of patient-rated xerostomia, 135 out of 136 patients at risk (99%) returned the questionnaire at 6

months. The compliance at 12 months after radiotherapy was 116 out of 122 patients at risk (95%). Of the 141 patients available for analysis of patient-rated sticky saliva, 117 out of 118 patients at risk (99%) returned the questionnaire at 6 months. The compliance at 12 months after radiotherapy was 100 out of 106 patients at risk (94%).

Dose distribution in the salivary glands

For all patients, the mean MD_{parb} was 41.7 Gy (SD:12.5Gy). The mean MD_{subb} was 56.8 Gy (SD: 10.1 Gy) and the mean MD_{oral} 28.5 Gy (SD: 19.4 Gy). In Table 2, the mean doses in the salivary glands stratified by treatment group are listed. In all salivary glands, the mean dose in the combined modality group was significantly higher as compared to the radiotherapy alone group.

Table 2: Comparison of dose parameters in organs at risk stratified by treatment modality.

Salivary gland	Mean dose (SD) in Gy		p-value
	RT alone	RT + CHT	
Mean dose in both parotid glands	38.4 (13.3)	50.7 (11.6)	p<0.001
Mean dose in ipsilateral parotid gland	40.8 (14.9)	52.3 (12.9)	p<0.001
Mean dose in contralateral parotid gland	36.6 (11.7)	49.0 (11.2)	p<0.001
Mean dose in both submandibular glands	55.3 (11.4)	65.8 (8.2)	p<0.001
Mean dose in ipsilateral submandibular gland	55.1 (10.7)	65.4 (8.8)	p<0.001
Mean dose in contralateral submandibular gland	55.7 (10.2)	66.1 (7.8)	p<0.001
Mean dose in oral cavity	26.4 (19.3)	35 (19.5)	p=0.012

Abbreviations: RT = Radiotherapy; CHT = chemotherapy

Changes in mean scores of patient-rated xerostomia

At baseline, the mean score of xerostomia for all patients was 21.8 (95% CI: 16.9-26.6) on a scale of 0-100, significantly increasing to 68.1 (95% CI: 62.9-73.3) at 6 months and showing some recovery at 12 months to 60.4 (95% CI: 54-66.9).

Among patients treated with combined modality, the mean score for xerostomia was 20.5 (95% CI: 12.9-28.1), significantly increasing to 70.5 (95% CI: 62.6-78.4) at 6 months, 67.8 (95% CI: 55.0-80.6) at 12 months, which gradually decreased to 62.5 (95% CI: 42.9-82.1) at 24 months (Figure 1).

Among patients treated with radiotherapy alone, the mean score for xerostomia was 22.6 (95% CI: 16.3-28.9), significantly increasing to 66.7

(95% CI: 59.9-73.5) at 6 months and showing some recovery at 12 months to 57.6 (95% CI: 50.2-65). After twelve months no important changes were observed (Figure 1). No significant differences were noted between patients that received induction, concomitant and alternating chemoradiation.

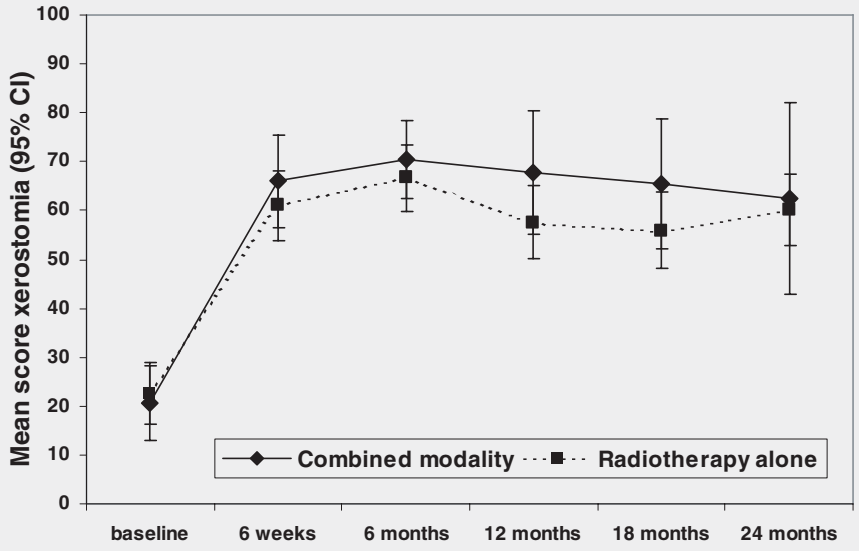

Figure 1. Mean scores of patient-rated xerostomia assessed with the EORTC H&N35 after radiation according to treatment modality (radiotherapy alone versus radiotherapy + chemotherapy).

Rates of patient-rated xerostomia

An event for $P_{xerostomia}$ was defined as an increase in xerostomia complaints after treatment from no or a bit before treatment to moderate or severe xerostomia thereafter. At 6 months, $P_{xerostomia}$ after combined modality was 66%, which did not significantly differ from that observed among those treated with radiotherapy alone in which $P_{xerostomia}$ was 65%. According to type of combined modality, $P_{xerostomia}$ was 53% after induction chemotherapy, 83% after concomitant chemoradiation 50% after alternating chemoradiation, but these differences were not statistically significant.

Table 3 : Results of the univariate logistic regression analysis with regard to moderate or severe xerostomia at 6 months.

Variable	Abbreviation	OR	(95% CI)	P-value
Mean dose both parotid glands (continuous) per 10 Gy	MD_{parb}	1.7	(1.24 - 2.33)	0.001
Mean dose both submandibular glands (continuous) per 10 Gy	MD_{subb}	1.08	(0.72 - 1.64)	ns
Mean dose oral cavity per 10 Gy	MD_{oral}	2.77	(1.43 - 5.33)	0.002
chemotherapy (yes or no)		1.03	(0.46 - 2.30)	ns
induction chemotherapy (yes or radiation alone)		0.61	(0.20 - 1.88)	ns
concomitant chemoradiation (yes or radiation alone)		0.53	(0.12 - 2.31)	ns
alternating chemoradiation (yes or radiation alone)		2.67	(0.70- 10.1)	ns

Table 4 : Results of the multivariate logistic regression analysis with regard to moderate or severe xerostomia at 6 months.

Variable	OR	(95% CI)	P-value
Model 1			
Mean dose both parotid glands (per 10 Gy)	1.67	(1.09 - 2.56)	0.02
Chemotherapy (yes or no)	0.5	(0.19 - 1.36)	ns
Mean dose oral cavity (per 10 Gy)	1.62	(0.74 - 3.56)	ns
Chemotherapy* Mean dose both parotid glands (per 10 Gy)	0.97	(0.43 - 2.17)	ns
Model 2			
Mean dose both parotid glands (per 10 Gy)	1.65	(1.08 - 2.55)	0.02
Induction chemotherapy (yes or radiation alone)	0.44	(0.12 - 1.63)	ns
Concomitant chemoradiation (yes or radiation alone)	0.65	(0.13 - 3.34)	ns
Alternating chemoradiation (yes or radiation alone)	0.48	(0.10 - 2.25)	ns
Mean dose oral cavity (per 10 Gy)	1.51	(0.64 - 3.55)	ns

Dose distribution, treatment modality and $P_{xerostomia}$

In the univariate logistic regression analysis, no significant association was found between treatment modality and $P_{xerostomia}$ at 6 months (OR: 1.03 (95%-CI: 0.46 – 2.3); p=0.95). In addition no significant differences were found between the different combined modality regimens (Table 3). $P_{xerostomia}$ was only significantly associated with MD_{parb} (OR: 1.05 (95%-CI: 1.02-1.09; p=0.001) and MD_{oral} (OR: 2.77 (95%-CI: 1.43 – 5.33); p=0.002) (Table 3).

In the multivariate analysis, in which MD_{parb}, MD_{oral} and chemotherapy (yes or no) were entered as variables, only MD_{parb} remained significantly associated with $P_{xerostomia}$ (OR: 1.67 (95%-CI: 1.09-2.56); p= 0.02) (Table 4). In addition, no significant interactions were found between MD_{parb} and treatment modality, indicating that the relationship between the mean dose in the parotid glands and $P_{xerostomia}$ did not depend on treatment modality (Figure 2). An additional analysis was performed to

investigate the influence of the individual combined modality schemes on $P_{xerostomia}$. The only variable in this second analysis significantly associated with $P_{xerostomia}$ at 6 months was MDparb (OR: 1.65 (95% CI: 1.08-2.55); p= 0.02)(Table 4).

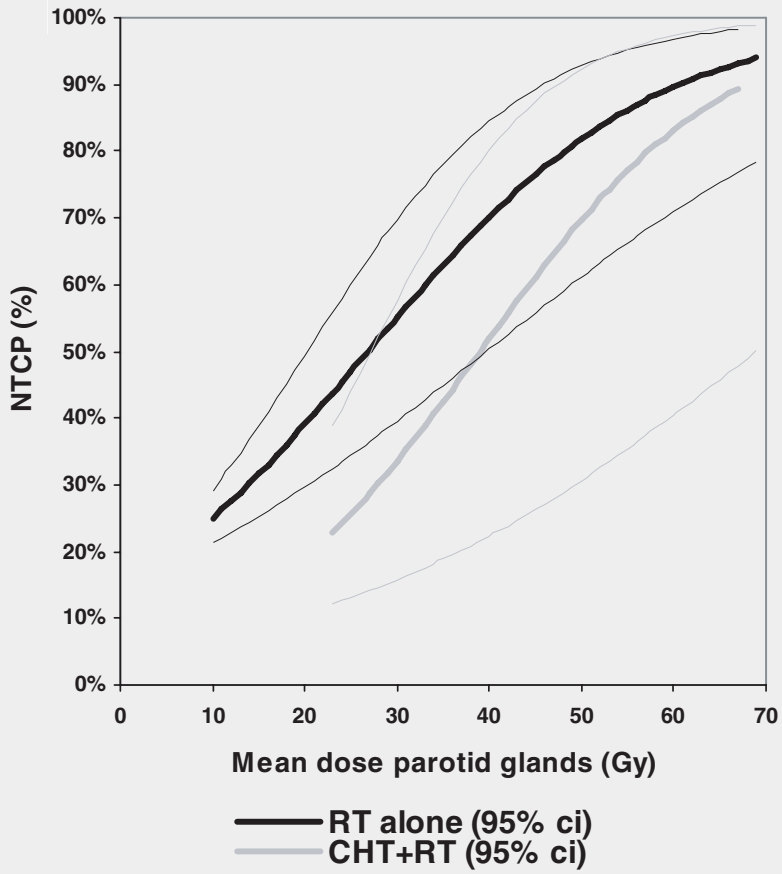

Figure 2: Probability of moderate or severe xerostomia as a function of the mean parotid dose. The black line indicates this relationship for patients treated with radiotherapy alone and the grey line for patients that received radiotherapy plus chemother

Changes in mean scores of patient-rated sticky saliva

At baseline, the mean score of sticky saliva for all patients was 19.4 (95% CI: 14.9-23.9) on a scale of 0-100, significantly increasing to 57.6 (95% CI: 51.9-63.3) at 6 months and showing some recovery at 12 months to 51.8 (95% CI: 45.5-58.1).

Among patients treated with combined modality, the mean score for sticky saliva was 20.5 (95% CI: 13.5-27.4), significantly increasing to 58.5 (95% CI: 49.1-67.9) at 6 months. After 6 months no important changes were observed (Figure 3).

Among patients treated without chemotherapy, the mean score for sticky saliva was 18.7 (95% CI: 12.9-24.5) at baseline, significantly increasing to 57.1 (95% CI: 49.9-64.3) at 6 months and showing some recovery at 12 months to 53.0 (95% CI: 46.0-60.0). After twelve months no important changes were seen (Figure 3).

The differences in the mean scores between the two groups were not statistically significant.

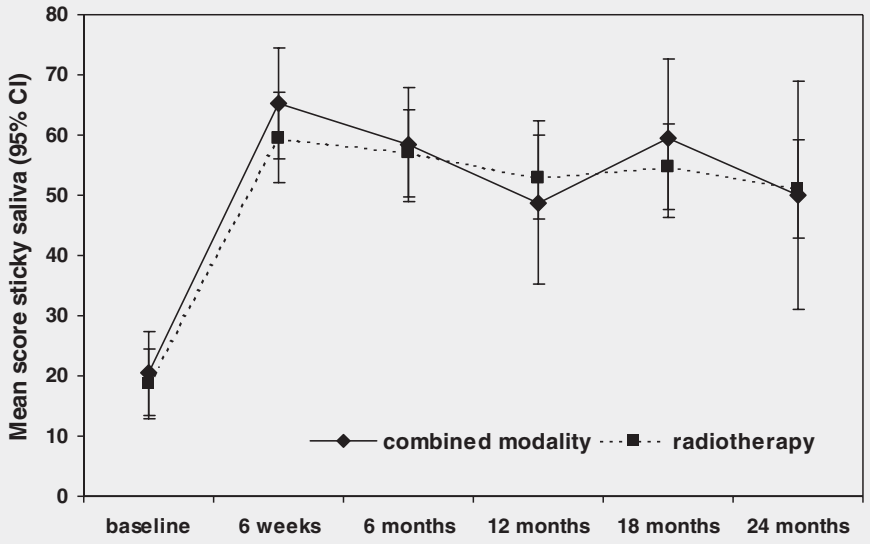

Figure 3. Mean scores of patient-rated sticky saliva assessed with the EORTC H&N35 after radiation according to treatment modality (radiotherapy alone versus radiotherapy + chemotherapy).

Probability rates of patient-rated sticky saliva

An event for $P_{\text{sticky saliva}}$ was defined as an increase in complaints of sticky saliva after completion of treatment from no or a bit before treatment to moderate or severe sticky saliva thereafter. At 6 months, $P_{\text{sticky saliva}}$ was 53% after combined modality, which did not significantly differ from to that observed among those treated with radiotherapy alone, in which $P_{\text{sticky saliva}}$ was 59%.

Dose distribution, treatment modality and patient-rated sticky saliva

In the univariate logistic regression analysis, no significant association was found between $P_{sticky\ saliva}$ and treatment modality (OR: 1.30 (95%-ci: 0.61-2.80); p=0.50) or with the individual combined modality schemes (not shown).

In the multivariate analysis, in which the same prognostic factors were entered as described for xerostomia, no significant interactions were found between the mean dose in any of the salivary glands and treatment modality, indicating that the relationships between the mean doses in the salivary glands and $P_{sticky\ saliva}$ did not depend on treatment modality. No other prognostic factors were found with regard to $P_{sticky\ saliva}$.

Discussion

This study was performed to investigate whether the addition of chemotherapy to radiation in the treatment of head and neck cancer patients increased the risk of developing xerostomia and sticky saliva. No significant relationships were found between treatment modality and $P_{xerostomia}$ or $P_{sticky\ saliva}$. In addition, no differences were found between patients that received combined modality and those that received radiotherapy alone, with regard to the mean values of the xerostomia and sticky saliva scale. The mean dose to the parotid gland proved to be the most significant factor for the risk of developing patient-rated moderate or severe xerostomia and this risk is not significantly further increased by the addition of chemotherapy.

It has to be stressed that this was not a randomised study and that the two treatment groups significantly differed with regard to a number of pre-treatment tumour and patient characteristics. In addition, patients that received combined modality treatment had significantly higher mean doses in all salivary glands as compared to those that were treated with radiotherapy alone (Table 2). Based on these higher doses in the combined modality group, we expected to see higher rates of xerostomia and sticky saliva in this group, which was however not the case. A probable explanation for this negative outcome is that the mean dose administered to the parotid glands was already far beyond the threshold dose. In literature, a threshold dose of 22.5-43 Gy has been reported, above which most patients will develop xerostomia.[23,24,25,27,32,33] This is reflected by the fact that the percentage of patients complaining of moderate or severe xerostomia in both groups was relatively high and

not significantly different. These results indicate that when the parotid glands already receive a high radiation dose, MD_{parb} predominantly determines the risk of developing xerostomia in patients treated with combined modality.

As far as we know only one other study reported on the risk of xerostomia in patients treated with combined modality. Kosuda et al[39] described a deterioration in salivary gland function as measured by scintigraphy in patients treated with combined modality compared to patients treated with radiotherapy or chemotherapy alone. However, this study included only 30 patients with mainly (80%) lymphoma. These patients were treated with a lower radiation dose, usually below 30 Gy, and different chemotherapy regimens as compared to the head and neck cancer patients included in the present study.

The patients in this study were treated with 3D-conformal radiotherapy and not with IMRT. It remains unclear to which extend our results can be extrapolated to head and neck cancer patients treated with IMRT. IMRT is highly conformal and thus able to treat the tumour to a high dose while sparing critical organs. With a lower mean dose to the parotid glands in IMRT treated patients the addition of chemotherapy may become of importance in the risk of getting moderate or severe xerostomia. Also in other modalities to spare the salivary glands, like transposition of the submandibular gland,[40] the relative contribution of the addition of chemotherapy to irradiation may be of importance.

Besides xerostomia, sticky saliva is a frequently reported side effect of radiation, which is irreversible in a considerable proportion of patients. In this study, similar to what was found for patient-rated xerostomia, no effect of the addition of chemotherapy was seen in patients treated with already a high dose of radiotherapy.

In conclusion, in patients treated with combined modality, the addition of chemotherapy does not increase the risk of treatment-induced moderate and severe xerostomia and sticky saliva when the salivary glands already receive a radiation dose above threshold. In these patients the risk of developing xerostomia is predominantly determined by the mean dose to the parotid gland.

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Chapter 6

Radiotherapy alone versus radiotherapy with Amifostine 3 times a week versus radiotherapy with Amifostine 5 times a week: a prospective randomized study in squamous cell head and neck cancer

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Abstract

Background: The main objective of this study was to investigate whether non-daily intravenous administration of Amifostine, was as effective as daily intravenous administration with regard to the reduction of the incidence of grade ≥ 2 xerostomia.

Material and methods: 91 patients treated with bilateral irradiation for head and neck cancer were included. Thirty-one patients received no Amifostine (AMI-0), 30 received Amifostine 200 mg/m^2 3 times a week (AMI-3) and 30 patients received Amifostine 200 mg/m^2 daily (AMI-5). Acute and late xerostomia and Quality of life (QOL) were assessed at baseline, 6 weeks, and every 6th month from 6 months to 24 months post-radiotherapy.

Results: Grade ≥ 2 late xerostomia differed significantly at 6 months (AMI-0 74% vs. AMI-3 67% vs. AMI-5 52%, (p=0.03)), but not thereafter. During follow up, patient-rated xerostomia deteriorated more in AMI-0 patients (mean difference score (MDS) 52) compared to AMI-3 (MDS 25) and AMI-5 patients (MDS 29), (p=0.01). Nausea and vomiting were reported most frequently as side effect, but > grade 2 toxicity was observed in only 4 patients. However, 28% of the patients discontinued Amifostine administration before the end of radiotherapy.

Conclusions: long-term patient-rated xerostomia is similar for AMI-3 and AMI-5. For late xerostomia the same effect is seen at 6 months but not thereafter.

Introduction

Radiotherapy is an important primary and adjuvant treatment modality in patients with head and neck cancer. Despite the beneficial effects with regard to loco-regional tumour control, the radiation dose that can be administered is limited. Salivary dysfunction is an important side effect of radiotherapy leading to xerostomia after irradiation in the head and neck area. The tolerance dose for damage to the parotid glands is approximately 26-40 Gy.[1,2,3] Below this dose, salivary dysfunction may be reversible. Higher doses may lead to irreversible damage of the salivary glands with permanent dryness, in particular in case of doses exceeding 60 Gy.[4,5,6]

To increase the therapeutic ratio, it could be worthwhile to enhance the radioresistance of normal tissues, without inducing protection of the tumour to radiation. Preclinical data supported that Amifostine could possibly be used as radioprotector because its radioprotective properties in normal tissues turned out to be higher compared to tumour cells.[7]

Amifostine is a thio-organic compound that was originally developed as a protector against radiation-induced toxicity in the event of nuclear war. Amifostine and its active metabolite, WR-1065, accumulate in many epithelial tissues with the highest concentrations found in the salivary glands, spleen and kidneys.[8] There are a number of normal tissues, which have been reported to be protected, particularly the salivary glands. In tumour bearing animals there was a selective cytoprotection of normal tissues from the irradiation without protection of the tumour.[9,10,11] Small clinical trials have suggested that Amifostine protects against radiation-induced xerostomia and mucositis.[12,13,14] Brizel and co-workers[15] conducted a large, prospective randomized multicenter trial for patients treated with radiotherapy for head and neck cancer. Patients were randomized to receive radiotherapy alone versus Amifostine (200 mg/m^2 i.v. over 3 minutes) prior to radiotherapy. The incidence of grade ≥ 2 acute xerostomia decreased from 78% without Amifostine to 51% with Amifostine ($p<0.001$), while the median dose at onset of xerostomia was 42 Gy without Amifostine and 60 Gy with Amifostine ($p=0.0001$). After two years, no significant difference on survival or tumour control was observed.

In most studies concerning radioprotection, Amifostine was used daily. The question arises whether non-daily administration of Amifostine could be as effective as daily administration. A less frequent schedule could be of importance for the usage of Amifostine in clinical

practice as the administration of Amifostine is labour and cost intensive. Several studies support the application of a non-daily scheme. First, Utley and co-workers demonstrated in mice that the half-life time of WR-1065 in salivary glands after intravenous injection was significantly longer compared to other tissues.[16] Secondly, in a randomized phase II trial, 39 patients with squamous cell carcinoma of the head and neck received adjuvant or primary irradiation (60 Gy, 2 Gy per fraction, and 5 times a week) with Carboplatin on days 1 to 5 and 21 to 25.[17] Twenty-five of these patients received 500 mg Amifostine infusions. Although Amifostine was only administered before Carboplatin on day 1 to 5 and day 21 to 25, patients treated with Amifostine experienced a significant reduction of radiation induced toxicity such as xerostomia, mucositis, dysphagia, loss of taste and dermatitis. Thus, although Amifostine was only given during part of the treatment, a reduction in radiation-induced toxicity was seen.

Therefore, the primary aim of this prospective randomized phase II study was to test the hypothesis that non-daily (3 times a week) intravenous administration of Amifostine is as effective as daily (5 times a week) intravenous administration of Amifostine with regard to the reduction of the incidence of grade ≥ 2 xerostomia compared to radiation alone.

Material and methods

Patients

Patients eligible for this study were those with stage III-IVB (UICC 1997)[18] squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and/or larynx, or those with lymph node metastases in the head and neck area from an unknown primary, treated with bilateral primary or postoperative radiotherapy with curative intent, a minimal life expectancy of 12 months and a WHO-performance score of 0-2. A good understanding of the Dutch language was required to be able to complete the quality of life (QoL) questionnaires. Furthermore, at the time of randomization, 75% of the parotid gland volume was expected to receive a radiation dose of at least 40 Gy. This was confirmed using CT-assisted treatment planning and dose-volume histograms (DVH). Excluded were patients with distant metastases (M1), previously irradiated patients, patients treated in combination with induction or concurrent

chemotherapy and patients with a tumour originating in the salivary glands. Pregnant patients, patients participating in another investigating trial and patients in poor general or psychological conditions not permitting the patient to complete the trial were also excluded. Because of the potential occurrence of hypotension after administration of Amifostine, patients with severe cerebrovascular disease, poor renal function or sustained hypotension not secondary to anti-hypertensive medication were also excluded. Written informed consent was obtained in all patients. The study was approved by the Medical Ethical Committee of the VU University Medical Center and is in accordance with the Helsinki declaration.

Study design

This was a prospective randomized phase II study, comparing radiotherapy alone with radiotherapy in combination with two different administration schedules of Amifostine. Patients were randomized to receive radiotherapy alone (AMI-0), radiotherapy in combination with Amifostine 200 mg/m^2, 5 times a week (AMI-5), before irradiation, or radiotherapy in combination with Amifostine 200 mg/m^2, 3 times a week (AMI-3), at Monday, Wednesday and Friday before irradiation. In case of accelerated radiotherapy (6 times a week with a second fraction on Fridays), Amifostine was only given before the first fraction on that day. Random assignment of patients was carried out at the department of Radiation Oncology of the VU University Medical Center, using a permuted block design. Patients were stratified by primary tumour site (oral cavity versus oropharynx versus others), radiotherapy (primary versus post-operative) and submandibular glands removed (yes versus no).

Administration of Amifostine

Amifostine was supplied in 10-mL single vials, containing 500 mg per vial. The lyophilized dosage was stored in a refrigerator (2°C to 8°C). Sterile 0.9% sodium chloride solution was used for reconstitution. Half an hour before administration of Amifostine, all patients were hydrated with 250 cc fluid orally. Amifostine was administered by slow intravenous (IV) injection over 3-5 minutes (200 mg/m^2), 15-30 minutes before irradiation, as it had been reported that administration in several minutes produces less acute toxicity compared to injection over 15 minutes.[19] During administration of Amifostine and for 15 minutes following administration,

patients were kept in supine position. Blood pressure was checked immediately before IV administration of Amifostine, immediately after IV administration of Amifostine and 10 minutes after administration. Prophylactic anti-emetic pre-medication was prescribed. Notations of all adverse events whether or not related to treatment were made.

Radiotherapy

Details on radiation therapy have been reported previously.[20] In brief, all patients were treated with megavolt equipment using isocentre techniques after 3D-planning. Generally, the initial target volume was irradiated using two opposing lateral fields with an anterior field to cover the lower jugular and supraclavicular lymph node areas. All patients received 46 Gy on elective treated areas; boost doses varied from 56 Gy (in case of negative surgical margins) to 63.5 Gy in case of lymph node metastasis with extranodal spread or positive margins. Those treated primarily with radiotherapy received 70 Gy on macroscopic tumour.

Endpoints

The primary endpoint of this study was ≥ grade 2 late radiation-induced xerostomia according to the RTOG/EORTC Late Radiation Morbidity Scoring Scheme.[21]

The secondary endpoints were: ≥ grade 2 acute radiation-induced xerostomia, patient-rated xerostomia and sticky saliva, QoL, loco-regional tumour control and survival.

Late radiation-induced xerostomia was assessed before radiotherapy and 6, 12, 18 and 24 months after completion of radiation. Acute radiation-induced xerostomia was scored according to the RTOG Acute Radiation Morbidity Scoring Criteria before, on a weekly basis during radiotherapy and up to 6 weeks after radiotherapy.

Assessment of quality of life and patient-rated xerostomia

For the evaluation of quality of life, the EORTC (European Organization for Research and Treatment of Cancer) Core Questionnaire (QLQ-C30 version 3.0) was used with the supplemental head and neck specific module, the QLQ-H&N35.[22,23]

To assess self-reported xerostomia, sticky saliva and other head and neck symptoms, the EORTC QLQ-H&N35 was used.[23] Patients rated their symptom score on a 1-4 scale (no-mild-moderate-severe), which was linearly converted to a 0 to 100 metric. Higher scores represent a

greater degree of symptoms.[24]

The questionnaire was administered before the start of treatment (baseline), and subsequently 6 weeks, and with 6 months interval from 6 months to 24 months after completion of radiation. Patients were asked to participate in the study during the first visit at the Radiotherapy department. After informed consent was obtained, the questionnaires were distributed to the patients who were asked to fill in the questionnaire at the same time. During the regular follow up visits, the patients were asked by a research nurse to fill in the questionnaires before visiting the physician. When a patient did not comply with the planned visit, the questionnaires were sent by mail. When the questionnaires were not returned within 4 days, the patient was telephoned and asked to complete and return the questionnaires.

For the purpose of this study, the effect of Amifostine on the self-reported symptom scales xerostomia and sticky saliva were considered most important. The other QoL dimensions were analyzed on an exploratory basis.

Loco-regional tumour control and survival

Loco-regional control (LRC) was defined as no tumour recurrence above the clavicles within the irradiated area. LRC and overall survival were calculated from the first day of radiotherapy.

Statistics

Based on the results of the study of Brizel and co-workers,[15] it was expected that the incidence of ≥ grade 2 xerostomia would be reduced from 75% to 50% when radiotherapy was combined with Amifostine (AMI-5). A similar reduction rate was expected from AMI-3 compared to AMI-0. With a 70% power to detect such a difference at the 5% significant level, 30 patients in each arm were required. The analysis was performed according to the intention-to-treat principle.

To test differences between treatment arms regarding the primary endpoint, i.e. the frequency of ≥ grade 2 late radiation-induced morbidity, the chi-square test was used.

In the univariate analysis, LRC and OS were estimated with the Kaplan-Meier method. To test the statistical significance of differences between curves, the log rank test was used.

Changes in symptoms and QoL items were evaluated with a repeated measurement ANOVA using a mixed effect modeling procedure, SAS

Proc. Mixed. In contrast to a "complete cases analysis", the mixed effect modeling retains in the analysis patients who dropout during follow-up. Trends over time for dropouts and complete cases are estimated under the assumption that patients within the same group have the same pattern over time. SAS Proc. Mixed uses the method of restricted maximum likelihood to estimate the parameters of the model. F-test was used for testing main effects of group and time, and the interaction effect of group x time.

Results

Patients

The study was open for inclusion from August 1999 to August 2003. Ninety-one patients were included, 30 patients in the AMI-3 and AMI-5 arms and 31 in the AMI-0 arm. The demographic and tumour characteristics of the population are listed in Table 1. No significant differences were noted between the three treatment arms. Sixty-seven percent of the patients were male. The mean age at the start of radiotherapy was 55 years, ranging from 24 to 73 years. Nearly half of the tumours originated in the oropharynx (46%). The majority of the patients received postoperative irradiation (78%).

The mean "mean dose" in the parotid glands was 43.5 Gy (95% CI:

Table 1. Patient characteristics.

	AMI-0 (N= 31)		AMI-3 (N= 30)		AMI-5 (N= 30)		Total (N=91)		p-value
Variable	Number	%	Number	%	Number	%	Number	%	
Sex									ns
Female	13	42%	10	33%	8	27%	31	33%	
Male	18	58%	20	67%	22	73%	60	67%	
Type of radiation									ns
Primary	3	10%	8	27%	2	6%	13	14%	
Postoperative	26	84%	20	67%	25	84%	71	78%	
Other	2	6%	2	6%	3	10%	7	8%	
T-classification									ns
T1	1	3%	2	7%	2	7%	5	6%	
T2	6	20%	6	20%	9	30%	21	23%	
T3	16	52%	11	37%	6	20%	33	36%	
T4	7	23%	9	9%	9	30%	25	27%	
N-classification									ns
N0	12	39%	7	23%	4	13%	23	25%	
N+	19	61%	23	77%	26	87%	68	75%	
Site									ns
Oral cavity	6	20%	9	30%	11	37%	26	29%	
Oropharynx	17	57%	14	46%	10	33%	41	46%	
Larynx	6	20%	3	10%	3	10%	12	13%	
Unknown primary	1	3%	2	7%	4	13%	7	8%	
Other	0	0%	2	7%	2	7%	4	4%	

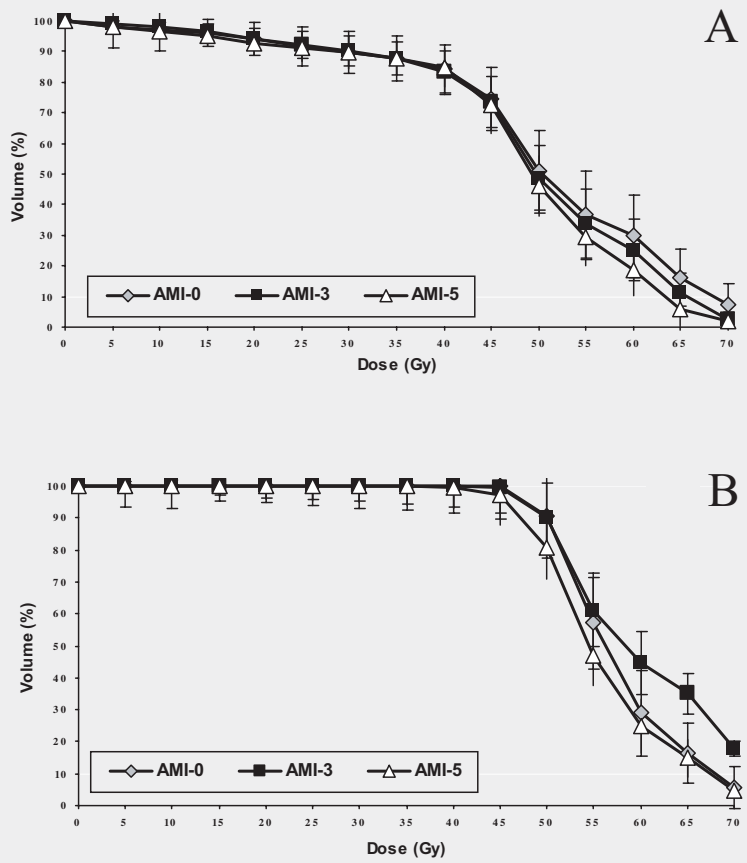

Figure 1: Mean dose-volume histograms of (A) parotid and (B) submandibular glands according to treatment arm.

Table 2. Side effects related to Amifostine (grading: CTCAE v3.0).

Side effect	Grade	AMI-0 (n=31)		AMI-3 (n=30)		AMI-5 (n=30)		chi square
		N	%	N	%	N	%	
Nausea	**Grade 1-4**	3	10%	9	29%	14	47%	p=0.004
	Grade ≥3	1	3%	1	3%	2	7%	ns
Vomitting	**Grade 1-4**	0	0%	2	6%	8	27%	p=0.016
	Grade ≥3	0	0%	0	0%	0	0	ns
Hypotension	**Grade 1-4**	0	0%	1*	3%	1*	3%	ns
	Grade ≥3	0	0%	0	0%	0	0%	ns
Allergic reaction	**Grade 1-4**	0	0%	2	6%	2	7%	ns
	Grade ≥3	0	0%	0	0%	0	0%	ns

* Not amifostine related

37.3-49.7) in the AMI-0 patients, 49.2 Gy (95% CI: 45.9-52.5) in the AMI-3 patients and 47.9 Gy (95% CI: 44.8-52.0) in the AMI-5 patients and differed not significantly (p=0.173).

The mean "mean dose" in the submandibular glands was 57.3 Gy (95% CI: 54.4-60.2) in the AMI-0 patients, 59.9 Gy (95% CI: 56.6-63.3), in the AMI-3 patients and 55.9 Gy (95% CI: 52.3-59.5) in the AMI-5 patients and differed not significantly (p=0.162). No differences were observed regarding the mean dose volume histograms in the parotid and submandibular glands between the three treatment arms (Fig 1A and 1B). Two patients were treated off protocol: one patient developed lymphangitis carcinomatosa on the second day of treatment, another patient developed pulmonary metastases during radiotherapy. All other patients completed radiotherapy as planned.

Side effects and compliance of Amifostine

Among the patients treated with Amifostine, minor side effects were seen (Table 2). Nausea and vomiting were reported most frequently during radiotherapy and occurred more frequently among those treated with Amifostine (p=0.004). Although there was a trend towards more nausea and vomiting in the AMI-5 arm compared to the AMI-3 arm, this was not significantly different (p=0.183). Other, less frequently reported side effects were hypotension and allergic skin reactions. Hypotension was often mild and of short duration. A total of 24 patients (28%) discontinued Amifostine before the completion of radiotherapy (Table 2). No difference was seen between AMI-3 and AMI-5. Nineteen patients (21%) discontinued Amifostine before receiving 40 Gy. Of the 24 patients that discontinued Amifostine, the most frequently reported reason was nausea and vomiting (15 patients). Other reasons for discontinuing Amifostine were allergic skin reactions in 4 patients, hypotension (not Amifostine related) in 2 patients, tumour progression in 1 patient, difficulties in accessing the vene in 1 patient and refusal in 1 patient.

Late radiation-induced xerostomia at 6, 12 and 24 months

At 6 months, the scores for late xerostomia according to the RTOG criteria differed significantly for the three study arms (p= 0.03). In the AMI-0 arm, 74% of the patients reported ≥ 2 grade late xerostomia versus 67% in the AMI-3 arm and 52% in the AMI-5 arm (Table 3). In the AMI-5 arm, 15% of the patients had no xerostomia, which was not the case in

Table 3. Incidence of late radiation-induced xerostomia.

Arm	6 months	12 months	18 months	24 months
AMI-0	20/27 (74%)	15/22 (68%)	13/20 (65%)	11/19 (58%)
AMI-3	18/27 (67%)	13/22 (59%)	8/16 (50%)	8/14 (57%)
AMI-5	15/29 (52%)	15/27 (56%)	12/21 (57%)	11/15 (73%)
P-value (DF: 2)	p=0.03	p=0.24	p=0.59	p=0.81

the other two treatment arms. After 12 months, no significant differences were noted between the three treatment arms. Furthermore, no significant differences were noted when AMI-0 was compared to all patients treated with Amifostine (AMI-3 and AMI-5).

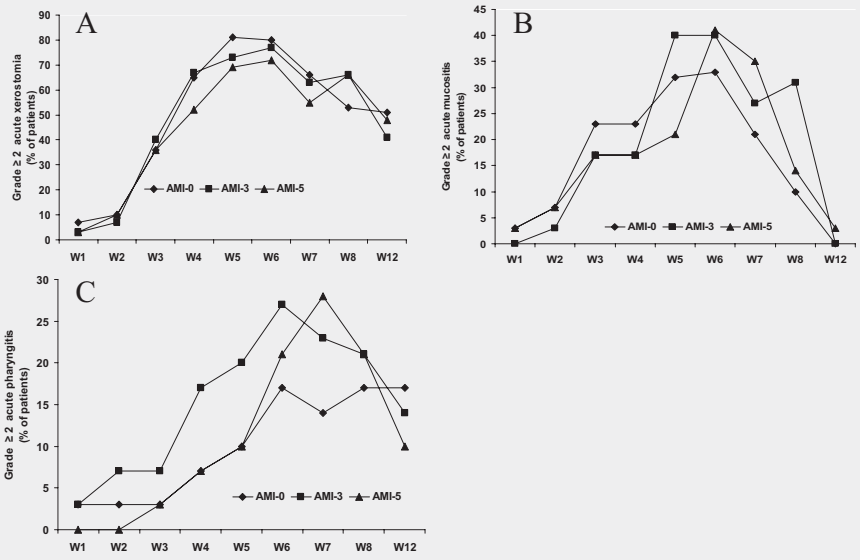

Figure 2: Incidence of grade ≥2 acute xerostomia (A), grade ≥ 3 acute mucositis (B) and grade ≥ 3 pharynx/esophagus toxicity (C) during and after radiotherapy. (Repeated measurement ANOVA: p=0.93 (A) and p=0.22 (B and C).

Acute radiation-induced reactions

At baseline, no significant differences were present between the three arms with regard to scores for xerostomia according to RTOG-criteria. Xerostomia was present in 3% of the AMI-0 and AMI-3 patients and in

13% of the AMI-5 patients (n.s.). In all three treatment arms, xerostomia increased to grade 2 at the end of treatment (AMI-0: 80%, AMI-3: 77% and AMI-5: 73%). Time of onset of acute xerostomia did not differ significantly between arms (Figure 2A). No significant differences were observed between the 3 treatment arms with regard to acute toxicity of the mucous membranes and pharynx (Figure 2B and 2C).

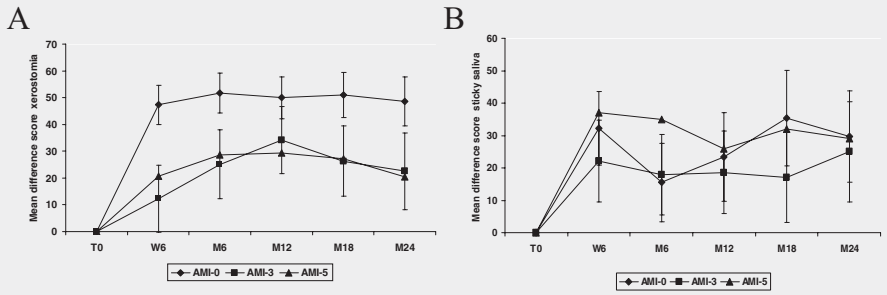

Figure 3: Mean difference scores of patient-rated xerostomia (A) and sticky saliva (B) measured with the EORTC QLQ-H&N35. Higher scores represent more complaints relative to baseline (Respectively p=0.016 and p= 0.47).

Changes in patient-rated xerostomia and sticky saliva

At baseline, no significant differences were noted with regard to patient-rated xerostomia and patient-rated sticky saliva. During follow up, the deterioration of patient-rated xerostomia among AMI-0 patients was significantly worse as compared to that among AMI-3 and AMI-5 patients (Figure 3A) (p=0.016).

The addition of Amifostine did not have any effect on patient-rated sticky saliva (Figure 3B). No significant differences between the three treatment arms were noted with regard to the other QoL dimensions (details not presented).

Survival and loco regional control

The 2-years LRC rate was 79% among AMI-0 patients, 67% among AMI-3 patients and 83% among AMI-5 patients (p=0.31; Figure 4A).

The overall survival at two years was 70% among AMI-0 patients, 84% among AMI-3 patients and 58% among AMI-5 patients (p=0.26; Figure 4B).

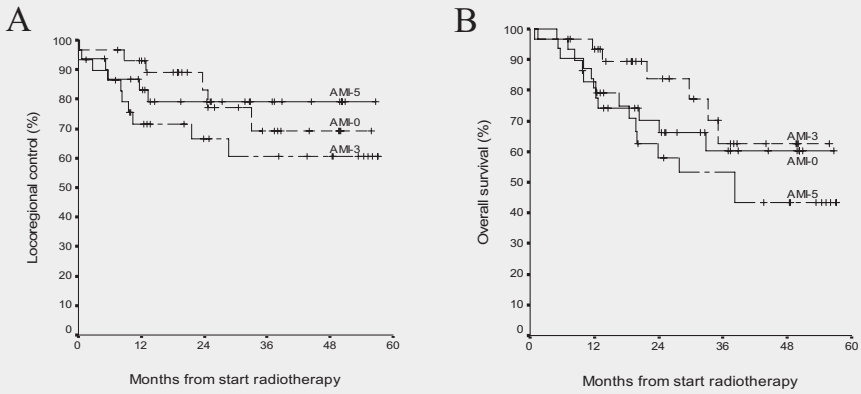

Figure 4: Kaplan-Meijer estimates of loco-regional control (A) and overall survival (B) according to treatment group.

Discussion

This study is the first reporting on the effect of two different regimens of Amifostine in addition to radiotherapy. The results indicate that the addition of Amifostine, 5 times a week, to radiotherapy, temporarily reduced the incidence of late radiation-induced xerostomia according to the RTOG/EORTC criteria at 6 months, but not thereafter. The schedule of Amifostine, 3 times a week appeared to be less effective with regard to the incidence of late radiation-induced xerostomia. However, with regard to patient-rated xerostomia, significantly less deterioration was observed when Amifostine was added to radiotherapy at all time points tested and no difference was noted between AMI-3 and AMI-5.

A number of authors have reported on the application of Amifostine in head and neck cancer patients treated with radiotherapy.[13,14,17] The most important study on this subject was reported by Brizel and co-workers.[15] In that study, patients treated for head and neck cancer were randomly assigned to receive (postoperative) radiotherapy alone versus (postoperative) radiotherapy with Amifostine, 5 times a week. A significant reduction of acute and late grade ≥ 2 xerostomia was observed as well as a significantly higher unstimulated salivary gland output when Amifostine was added to radiation. Moreover, patients receiving Amifostine experienced a better clinical benefit, which was measured using a Patient Benefit Questionnaire.[25]

In our study, the acute xerostomia revealed no differences between the study arms. This could be explained by the fact that virtually all patients experienced serious sticky saliva and loss of taste, two factors

of influence on the rating of acute xerostomia according to the RTOG-criteria. It remains unclear whether loss of taste and sticky saliva were taken into account in the assessment of acute xerostomia in the study of Brizel et al.[15]

A number of authors found that the post-radiotherapy salivary gland function significantly depended on the dose distribution in the parotid glands. One of the main shortcomings of other studies reporting on the radioprotective properties of Amifostine is that the amount of salivary tissue included in the radiation portals was estimated based on the simulation films and not on 3D-information derived by plannings-CT scan. In the present study, the dose distribution in the salivary glands was evaluated using dose-volume histograms and no differences were observed regarding the mean dose and mean dose-volume histograms in the parotid and submandibular glands between the three treatment arms.

Most grading systems of xerostomia and endpoints in studies assessing dry mouth are based on functional disabilities.[21,26,27] However, in clinical practice, xerostomia is primarily a quality of life issue. A lack of concordance between objective endpoints of xerostomia like salivary flow and xerostomia-related questionnaires assessing patient-rated xerostomia has been reported.[5,28,29,30] Also the physician-rated RTOG toxicity score system, though widely used, has a potential lack of sensitivity, as it has not been validated prospectively. Therefore, patient-rated xerostomia was considered the most important end point.

In the present study, the EORTC QLQ-H&N35 was used to assess patient-rated xerostomia and sticky saliva. It is important to notice that this instrument contains only one question regarding xerostomia and one question regarding sticky saliva using 4-point Lickert scales. Subjective xerostomia is a complex symptom, which may vary during the day and may be more pronounced in a given situation such as speaking, eating and physical activity. Therefore, quality of life scales with few specific questions may not be sensitive enough. Recently Eisbruch etal.[30] described a validated xerostomia questionnaire containing 8 questions on xerostomia rated on an 11-point Likert scale. Such validated questionnaires, addressing different aspects of xerostomia and xerostomia-related symptoms may possibly enable to detect more subtle changes than the methods that were used in the present studies.

Although patients receiving Amifostine did significantly better with regard to patient-rated xerostomia than those who received radiotherapy

alone, this was not translated into better scores on more general QoL dimensions, nor on head and neck symptoms (data not shown). These results indicate that Amifostine mainly has a radioprotective effect on salivary gland tissue and not on other normal tissues such as the mucosa. This is supported by the lack of significant group differences in acute mucositis and acute toxicity of the pharynx. Furthermore, the results also indicate that prevention of xerostomia does not necessarily translate into improvement in the general QoL of patients, something that has often been suggested but never confirmed empirically.

One of the problems identified in the present study is the reduced compliance due to toxicity of Amifostine, in particular nausea and vomiting. Though toxicity scores were in the lower range and were considered mild, for many patients nausea and vomiting complaints were a serious burden, even after adjustment of the anti-emetic regimen. Oral correction of hydration status did not reduce nausea sufficiently in all patients. The toxicity due to Amifostine in our study is comparable to the study of Brizel etal. They reported 47% of Amifostine treated patients with any grade of nausea, 37% with any grade of vomiting, 15% with hypotension and 5% with an allergic reaction. This was reflected in a non-completion rate of 22%.[15] Also others have reported about reduced compliance due to the toxicity of Amifostine.[13,14,15,31] The level of treatment discontinuation varies from 11% to 41%, depending on the dose of Amifostine administered and the radiation scheme applied. One study was even ended preliminary due to toxicity.[31] Therefore, even though trials report prevention of xerostomia by intravenous administration of Amifostine pre irradiation, toxicity is an important obstacle in clinical practice. A decrease of the administration time of Amifostine by rapid IV push may further reduce toxicity.[32] Also delivering Amifostine subcutaneously may seem a new promising way of delivery, but even then a number of patients (11%) are reported to suffer from substantial toxicity and compliance is reduced by 10-35%.[33,34] The present study was started as a phase II study with the intention to proceed in a phase III study. However, due to smaller than expected differences between the treatment arms, the possibility of tumour protection[35] and the difficulties met with compliance, it was eventually decided not to proceed with a phase III study. Furthermore, the question arises if there is a place for radioprotective agents like Amifostine in the era of new technological developments in radiation oncology such as intensity-modulated radiation. A number of studies have indicated that the probability of radiation-induced xerostomia

depends primarily on the mean parotid dose[1,2] and/or mean submandibular dose[20] and that radiation-induced xerostomia can be prevented by the use of these newer techniques. Whether Amifostine could be of use in a specific subgroup of patients depending on the mean dose in the salivary glands requires further investigation.

In conclusion, despite only moderate levels of compliance, Amifostine offers temporary protection from late radiation-induced xerostomia, and a longer lasting effect on patient-rated xerostomia. The late radioprotective properties of a 3-times weekly dose of Amifostine appear to be similar to that of a 5-times per week schedule. However, toxicity may hamper implementation in clinical practice.

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Chapter 7

The efficacy of Xialine® in patients with xerostomia resulting from radiotherapy for head and neck cancer: a pilot-study

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Abstract

Changes in subjective sensations due to xerostomia before and after administration of Xialine®, a xanthan gum-based saliva substitute, were evaluated in 30 patients with radiation-induced xerostomia using the QLQ-H&N35. Xerostomia in general decreased with both Xialine® and placebo to almost the same degree. A trend was seen for Xialine® to improve problems with speech and senses.

Introduction

Radiotherapy is an important treatment modality in patients with head and neck cancer. In case of tumours localised in the oral cavity, oropharynx and nasopharynx, the parotid and submandibular glands and in some cases a large proportion of the minor salivary glands are included in the radiation portals potentially resulting in severe salivary gland dysfunction.[1] After radiotherapy, saliva production is decreased and its composition is altered.[2]

Xerostomia is an important complaint after radiotherapy leading to discomfort, dysphagia, abnormal swallowing patterns, difficulty in chewing and speaking, taste changes, increased dental caries risk and shifts in oral microbiological parameters. For those patients who have some residual salivary gland function, cholinergic agonists such as pilocarpine and nicotinamide may produce some symptomatic improvement.[3,4,5] However, in the majority of cases, xerostomia remains an important late side effect.[6] In these cases symptomatic relieve could be obtained by a saliva substitute.

A number of saliva substitutes have been developed during the last decades. These substitutes are mainly based on carboxymethylcellulose, polyethylene oxide or animal mucins.[7,8,9,10] In a recent study, the efficacy of polymer-based saliva substitutes, among others xanthan gum, was evaluated in patients with Sjögren's syndrome.[11] The xanthan gum based saliva substitutes were more effective than placebo with regard to subjective improvement of sicca symptoms. No data are available yet supporting the efficacy of these substitutes in patients with radiation-induced xerostomia.

The aim of this study was to investigate the efficacy of Xialine®, a polymer-based saliva substitute, with regard to subjective improvement of radiation-induced xerostomia and related symptoms in patients treated for head and neck cancer compared to placebo in a pilot-study.

Material and methods

Patients

Patients were eligible when they met the following inclusion criteria: subjective discomfort from xerostomia; previous irradiation for head and neck cancer which started more than 3 months before entering the study; at least 75% of the volume of the parotid glands received a dose

of 50 Gy or more and a WHO performance status 0-2. The volume of the parotid gland included in the radiation portals was estimated using simulation films. In all patients written informed consent was obtained. Patients were excluded in case of alcohol abuse (≥5 unit's daily) or in case of salivary dysfunction due to other causes, e.g. medication.[12] Approval from the institutional ethical board for this study was obtained.

A total number of 30 patients were included of which 19 were males and 11 females. The median age was 59 years, ranging from 46 to 79. Radiation took place between 1991 and 1998. The primary site was located in the oral cavity in 7 patients, the oropharynx in 8 patients, the supraglottic larynx in 9 and other sites in 4 patients. Two patients were treated for lymph node metastases with an unknown primary tumour. The median dose delivered at the primary tumour site was 62.7 Gy, ranging from 55.0 to 72.5 Gy. No differences were noted between the two treatment arms.

Study design

The study was set up in a randomised double-blinded, placebo-controlled, crossover design to detect differences in changes in radiation-induced xerostomia and xerostomia-related symptoms. The number of 30 patients was considered sufficient to get an impression of the differences between placebo and Xialine and subsequently to decide as to whether a larger randomised study should be initiated. The crossover design was chosen to limit the number of patients needed.

Patients were randomised to receive: (1) Xialine® for one week followed by a washout period of one week and one week placebo or (2) placebo for one week followed by a washout period of one week and one week Xialine®. The substitutes, either placebo or Xialine® had to be used at least 4 times a day. During the washout period, the use of any saliva substitute was not allowed. Treatment randomisation was carried out by the department of Pharmacy of the Academic Hospital Vrije Universiteit Amsterdam, providing numbered bottles that did not indicate the containing substance. Neither the patient nor the treating physician knew which treatment arm was allocated. Breaking of the key code took place after all patients completed the entire course of treatment.

Questionnaires

To assess xerostomia and related symptoms the head and neck cancer module EORTC QLQ-H&N35 was used.[13] This module contains 35

questions divided in 7 sub-scales and 11 single item scales. All scales are rated on a four-point Likert-scale. All sub-scales are linearly converted to a 0 to 100 scale. Higher scores represent a greater degree of symptoms.[14] The reliability and validity of these questionnaires have been confirmed in a number of international studies in cancer patients. [13,15,16]

In the analysis, only the scales regarded as most relevant for the purpose of the study were investigated, i.e. swallowing, decreased senses (smell and taste), problems with speech, social eating, dry mouth and sticky saliva.

Saliva substitute

Xialine® is a saliva substitute with visco-elastic properties closely resembling natural human saliva. The active visco-elastic component is the polysaccharide xanthan gum; additionally, sodium fluoride is included for mineralization of the dentition.[17] For the purpose of this study Xialine®gs was used, which is a variant of the normal Xialine® but without mint-taste. (Lommerse Pharma B.V., Oss, The Netherlands). The composition of the placebo was similar to Xialine®gs (from here denoted as Xialine®), but did not contain xanthan gum. Xialine® and placebo were applied with the same type of spray apparatus.

Statistics

In the present study all scales (1-4 Likert scale) were linearly converted to a 0 to 100 scale, according to the guidelines of the EORTC. In addition, the change score was calculated which was equal to the score assessed after 1 week of administration of Xialine or placebo minus the score at baseline. Differences in the changes of scores with time were tested with a repeated measures analysis of variance.

Patients were then classified as having ‘worse' symptoms when the change score increased with 5 points or more, as having ‘no change’ when the change score was less than 5 points and as having ‘improvement’ when the change score decreased with 5 or more. Differences in the rate of improvement were tested with a chi-square test.

Results

Twenty-nine patients completed the study. One patient withdrew in the first week because of nausea and was excluded from the analysis. The remaining 29 patients completed all questionnaires. In general, no

differences were noted with regard to the baseline values of the analysed scales on visit 1 and visit 3. Therefore, a one-week washout-period was considered to be sufficient. Xialine® was used with a mean frequency of 14 times a day, which was comparable to the frequency observed when the placebo was used (13 times per day). The order in which Xialine® and placebo were used did not affect the results.

Table 1: Change scores after one week use of Xialine® and placebo.

Scale	Mean score at baseline	Mean change score after Xialine® (SE)	Mean change score after placebo (SE)	P-value
Xerostomia	84	-14.8(4.0)	-17.2 (4.3)	0.78
Sticky saliva	71	-10.7 (7.7)	-11.5 (6.9)	0.43
Problems with speech	30	-7.1 (3.1)	-0.6 (3.1)	0.25
decreased senses	32	-6.3 (3.7)	-1.7 (3.6)	0.43
Swallowing	30	-2.9 (5.3)	-2.8 (3.2)	0.91
Social eating	27	-4.6 (1.8)	-3.6 (2.2)	0.65

SE= Standard error

Change of scores: Xialine® versus placebo

A marked improvement was noted for dry mouth and sticky saliva after both Xialine® and placebo. The change score for dry mouth was -17 with Xialine® compared to -15 with placebo (Table 1), which was not statistically significant. No difference was noted between Xialine® and placebo with regard to the change score for sticky saliva, which was -11 for both Xialine® and placebo (Table 1). Only minor changes were observed for the other scales investigated.

Table 2: Response rates after one week use of Xialine® and placebo .

Scale	% better after Xialine®	% better after placebo	p-value
Xerostomia	38	41	1
Sticky saliva	38	45	0.83
Problems with speech	45	21	0.05
Decreased senses	45	24	0.09
Swallowing	31	45	0.2
Social eating	45	38	0.61

Response rate: Xialine® versus placebo

A trend towards higher response rates after Xialine® was observed for problems with speech and decreased senses, compared to placebo (Table 2). The response rate for both scales was 45% after using Xialine® compared to 21% and 24% respectively after using placebo. No differences between Xialine® and placebo were noted with regard to xerostomia, sticky saliva and social eating.

Discussion

Xerostomia is an important symptom after radiotherapy in the head and neck area.[6] This study was performed to investigate whether the use of Xialine® resulted in a higher degree of improvement of xerostomia and xerostomia-related symptoms compared to the use of placebo. Higher response rates were observed after Xialine® with regard to problems with speech and decreased senses, while no important differences were noted with regard to xerostomia, sticky saliva and social eating. Both Xialine® and placebo resulted in a response rate of approximately 40% for these latter three scales, pointing out that with the administration of saliva substitutes in general, these complaints may improve in about 40% of the cases. In a number of other studies concerning patients with radiation-induced xerostomia, the response rates for subjective improvement with saliva substitutes varies between 47% and 56%.[3,18] The results in the present study appear to be somewhat lower, which may be explained by the fact that the assessment of subjective improvement in these studies was performed different from ours.

The only difference in composition between the placebo and Xialine® was the addition of xanthan gum. Xanthan gum containing saliva substitutes have synergistic effects on the elastic and rheologic properties of human whole saliva. The retention time of a fluid film on the oral mucosa may be enhanced by the elasticity of the substitute.[19] Based on these properties, xanthan gum containing substitutes should theoretically be more beneficial for use in patients with radiation-induced xerostomia. However, this was not reflected in differences regarding the frequency of administration and improvement of most symptoms.

The response rates observed for speech and senses were higher with xanthan gum than with placebo, although these differences were not statistically significant. However, this may be due to the relatively small number of patients.

A positive effect of Xialine has been reported before by Van der Reijden and co-workers in patients suffering from xerostomia due to Sjögren disease. In this category of patients, Xialine® as referred by patients with a low resting salivary flow rate.[11] In irradiated patients a comparable low flow rate is seen when at least 45 Gy was previously administered at all salivary glands during radiotherapy, like in our patients.[20,21]

Also other saliva substitutes are reported to relieve the symptoms related to xerostomia in irradiated patients to some extent, but not completely.[13] Davies and co-workers reported a stronger effect of pilocarpine mouthwash in patients with xerostomia due to radiation compared with the saliva substitute Saliva Orthana.[17] However, in contrast to our patients there might be some residual salivary gland function in part of these patients, which is a prerequisite for the effectiveness of pilocarpine on xerostomia.

We conclude from this study that xerostomia decreased with both Xialine® and placebo to almost the same degree. A trend was noted towards a higher degree of improvement of problems with speech and senses when Xialine® was used. However, the results do not support an additional value of xanthan gum-based saliva substitutes over other saliva substitutes among patients with radiation-induced xerostomia. The small differences observed do not support the design of a prospective randomised study to investigate whether Xialine® is of more benefit regarding the relief of radiation-induced xerostomia than other saliva substitutes.

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Chapter 8

General discussion

Radiotherapy has an established role in the treatment of patients with head and neck cancer, but side effects can be considerable and may lead to increased morbidity. Radiation-induced xerostomia is a long-lasting complaint and it is the most frequent and most important side effect experienced by patients.[1] Treatment of xerostomia is very difficult and often not successful. As the patient is the one with the disease,[2] ultimately, he or she is the one to balance the benefits of treatment against the harmful aspects of disease and therapy, so QoL should be an important aspect in decision-making. Many studies have investigated radiation-induced xerostomia with help of objective measurements like salivary flow. However, there is no clear correlation between objective and subjective measurements.[3,4] Therefore, in this thesis, we focus on xerostomia and sticky saliva as reported by patients. Four related issues are investigated: (1) the impact of xerostomia on QoL; (2) the role of radiation dose distribution parameters on the risk of developing patient-rated xerostomia and sticky saliva; (3) the effect of prevention with Amifostine and (4) treatment using Xialine®.

QoL

Although xerostomia is an important side effect of radiotherapy in head and neck cancer patients, data on the impact on QoL remain scarce. The results presented in this thesis show that xerostomia has a significant and clinically relevant impact on QOL and on the more general dimensions of QoL. An important finding is that although the incidence of moderate or severe xerostomia decreases with time, the impact on QoL increases. Thus, once a patient experiences xerostomia, this has an impact on his or her daily life, and for those who do not recover, this effect increases with time. These findings are important as they stress the necessity to prevent radiation-induced xerostomia.

Therapy

In irradiated salivary glands responsive to stimuli, pilocarpine may offer some relieve from xerostomia.[5,6] On the other hand, when there is no residual function of the salivary gland post treatment, xerostomia is usually resistant to therapy. The development of saliva substitutes offers no real solution to this problem. Our results are in line with other published studies. No significant effect on dry mouth symptoms is observed in general, although there appears to be a trend for Xialine® to improve problems with speech and senses. Since results of application

of saliva substitutes are generally disappointing, and pilocarpine only works in glands with some residual function, there is no good solution for persisting radiation-induced xerostomia. Therefore, the best treatment of xerostomia is prevention.

Prevention: Radiation parameters

There are several ways to reduce the risk of radiation-induced xerostomia. An important strategy is the usage of modern techniques: nowadays, most institutes use 3D- CT-based planning techniques, and IMRT is more and more integrated in daily practice. In this approach it is important to establish the impact of radiation parameters on the risk of developing xerostomia and sticky saliva.

Most studies investigating radiation-induced xerostomia focus on the parotid glands and used salivary flow as an endpoint.[7,8,9] To our knowledge, there is no information on patient-rated xerostomia and sticky saliva and relatively little attention has been paid to other salivary glands. Our study in bilaterally irradiated patients shows that the risk of developing radiation-induced patient-rated xerostomia not only depends on the mean dose to the parotid glands, but also on the mean dose to the submandibular glands. Thus, to reduce the risk of patient-rated xerostomia, it is not only important to spare the parotid glands, but the dose to the submandibular glands has to be taken into account as well and kept as low as possible. This implies that next to the parotid glands, the submandibular glands need to be delineated and should be considered as organs at risk. In patients treated with IMRT this means that also dose constraints should be used for the submandibular glands.

Our studies show that the prediction of patient-rated xerostomia is even more complicated. The results demonstrate that the mean dose to the contralateral parotid gland is more relevant than the mean dose in the ipsilateral parotid gland with regard to the probability of radiation-induced patient-rated xerostomia. In most studies, the parotid glands are considered as a single organ. From this point of view, it turns out that the most effective way to prevent patient-rated xerostomia is to exclude the contralateral neck from the target volume. In this respect, identification of patients with a low probability on contralateral lymph node metastases becomes increasingly important. Unilateral radiotherapy for e.g. well lateralized tonsillar cancer has shown very low (<3.5%) contralateral neck recurrence without compromising loco-regional control.[10,11] The reported incidence of xerostomia is low, 9%.[10] Therefore,

unilateral radiotherapy seems a promising option in selected cases.

In addition, we have studied the risk of developing patient-rated sticky saliva. In bilaterally treated patients, this risk is only determined by the mean dose to the submandibular glands and not by the mean dose to the parotid glands. Hence, for sticky saliva only the submandibular glands are regarded as organs at risk. In unilaterally treated patients, the mean dose to the contralateral submandibular gland is more important then the mean dose to the ipsilateral submandibular gland. Both glands should not be considered together as a single organ. Thus, in order to keep the risk of radiation-induced patient-rated sticky saliva as low as possible, here it is also important to exclude the contralateral neck from the target volume when possible.

The question arises as to whether and how our results should be translated to patients treated with IMRT. Although IMRT is able to treat the tumour to a high dose while sparing critical organs, this goes together with a highly inhomogeneous dose distribution. The location of the hotspots and lower dose regions may impact the dose distribution in the salivary glands; sparing the parotid gland may thus lead to higher dose in the oral cavity and submandibular glands. Our results suggest that the dose to the oral cavity is not significant for the risk of developing xerostomia, but the effect of such an inhomogeneous dose distribution is unclear. Eisbruch et al.[3] has observed an impact of the mean oral cavity dose on the risk of radiation induced xerostomia, but in this study patients were treated with 3D conformal radiotherapy as well as with IMRT.

Considering combined modality, chemotherapy does not seem to increase the risk of xerostomia. Yet, the mean dose to the parotid glands in both treatment arms is already above the threshold for xerostomia. Therefore, an additional effect of chemotherapy on the risk of developing xerostomia cannot be excluded.

The results in this thesis show that it is difficult to predict who will suffer from patient-rated radiation-induced xerostomia and sticky saliva. The model is dependent on the endpoint chosen (xerostomia or sticky saliva) and treatment related parameters like treatment technique and organs at risk. Furthermore, who will suffer to what extend is also complicated to see at forehand as our study on the impact of xerostomia showed that the impact was different according to sex (larger effect in females) and age (larger effect in young patients).

Prevention: Amifostine

Another strategy to prevent radiation-induced xerostomia is the administration of Amifostine during radiotherapy. In our study, a protective effect of Amifostine from late radiation-induced observer-rated xerostomia is observed at 6 months, and a longer lasting effect on patient-rated xerostomia as measured during 2-year follow up. The late radioprotective properties of a 3-times weekly dose of Amifostine appear to be similar to that of a 5-times per week schedule. Although Amifostine has a positive effect on radiation-induced xerostomia, toxicity is a major problem, as has been seen with others.[12,13,14] This may hamper implementation in clinical practice. Investigation of alternative administration techniques, adequate hydration and more anti-emetic regimens may lead to reduced acute toxicity and may increase compliance.

There has been considerable debate about Amifostine, as tumour-protection has been described in the pre-clinical setting.[15] Individual clinical trials showing protection of normal tissue by Amifostine are too small to exclude any effect of Amifostine on tumour treatment. In a recent meta-analysis no signs of tumour protection are found.[16] Now, the question arises whether the addition of Amifostine to other parotid sparing techniques, like IMRT and submandibular gland transfer may lead to a further reduction in radiation-induced xerostomia. Up until now no studies on the use of Amifostine in combination with these techniques have been published.

Conclusions

- Xerostomia has a significant and clinically relevant impact on QoL and on the more general dimensions of QoL. As a consequence, it affects daily life.
- In many patients dry mouth symptoms do not recover and treatment is relatively ineffective. Saliva substitutes like Xialine® proof no real answer to radiation-induced xerostomia.
- Therefore, as we showed a clear impact of xerostomia on QoL, it is important to prevent radiation-induced xerostomia.
- In this thesis, we show that it is complicated to predict which patients will suffer from patient-rated xerostomia and patient-rated sticky saliva. Chosen endpoint, treatment technique and mean dose to organs at risk influence the process. The submandibular glands should be considered as an organ at risk in treatment planning of head and neck cancer patients in trying to reduce the

risk of patient-rated xerostomia and sticky saliva. In unilaterally treated patients, the mean dose of the salivary glands should be observed separately. Furthermore, the severity of the impact of xerostomia is difficult to predict as it is influenced by patient-depended factors such as age and sex.

- Regarding prevention by selective drugs, we showed a protective effect of Amifostine on xerostomia. However, the definitive value of Amifostine in the prevention of radiation-induced xerostomia still has to be established in this era of new treatment techniques like IMRT.

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Chapter 9

Summary

Summary

In *chapter 1*, the general introduction, an overview is presented of radiation-induced dry mouth, its relation with radiotherapy parameters, the methods to assess xerostomia, the relation with QoL and research on therapy and prevention. Despite many efforts, xerostomia is still a very common, troublesome and usually therapy-resistant side effect for head and neck cancer patients treated with radiotherapy.

Quality of life

Saliva plays an important role in many aspects of daily life. Therefore, it is often assumed that a reduced salivary flow may have an impact on QoL. In *chapter 2*, the results are presented of a prospective study in which we investigated the impact of xerostomia on QoL. In this study we used the RTOG late toxicity score system as a measure to assess xerostomia. The results of this prospective study are the first that showed a significant impact of radiation-induced xerostomia on QoL and on xerostomia-related dimensions. With increasing xerostomia grade a decrease in functioning scales is seen as well as an increase in the symptoms of insomnia and fatigue. This effect is more pronounced in female and younger patients. Furthermore, though the incidence of xerostomia decreases with time, the impact of a dry mouth on QoL increases.

Radiation parameters

Studies on radiation-induced xerostomia have primarily focused on the role of the parotid gland. However, saliva is also produced by other salivary glands. Irradiation of these glands may affect the risk of development of radiation-induced xerostomia as well. In *chapter 3*, the relation between the mean dose of the parotid glands, the submandibular glands and the minor salivary glands lining the oral cavity and the risk of developing radiation-induced patient-rated xerostomia and sticky saliva is described. We showed that the mean dose of the parotid glands as well as the mean dose of the submandibular glands influences the risk of developing subjective complaints of moderate or severe xerostomia. This risk as a function of the mean parotid dose is influenced by the mean dose to the submandibular gland, i.e. with increasing mean submandibular dose a lower dose to the parotid gland is needed to cause the same degree of xerostomia. No significant effect of the mean dose of the oral cavity was seen. Patient-rated sticky saliva mainly depends on the dose

in the submandibular glands and shows some recovery over time.

Most studies concerning radiation and xerostomia involve patients treated with bilateral irradiation. However, in some patients, e.g. in those with T1 or T2 tonsillar carcinoma, radiation can be limited to the ipsilateral neck, without compromising loco-regional control. In *chapter 4*, the relationship between the mean dose in the salivary glands and xerostomia among patients treated with unilateral irradiation as compared to patients treated with bilateral irradiation is described. The risk of developing patient-rated moderate or severe xerostomia and sticky saliva is significantly worse after bilateral compared to unilateral irradiation. After unilateral irradiation, patient-rated xerostomia and sticky saliva recovered to the baseline level. The probability on moderate or severe xerostomia is not only determined by the mean parotid dose, but also on the technique used. When focussing on the individual glands, the mean dose of the contralateral parotid gland is the only factor relevant for the risk of developing patient-rated moderate or severe xerostomia. No significant role of the mean dose of the oral cavity or the mean dose of the submandibular glands was observed, neither for the risk of patient-rated xerostomia nor for the risk of patient-rated sticky saliva.

Combined modality

In *chapter 5*, the effect of combined modality, in casu chemotherapy and radiotherapy, on the risk of developing radiation-induced patient-rated xerostomia is described. For this study 148 patients were eligible, 93 treated with radiotherapy and 55 treated with chemotherapy and radiotherapy. In this study, the addition of chemotherapy does not significantly further increase the risk of developing xerostomia in patients treated with radiotherapy. Only the mean dose in the parotid gland plays a significant role. Though, the univariate analysis according to treatment arm suggests that chemotherapy may be of some importance as patients in the combined modality group have a higher odds ratio, i.e. a higher risk per 1 Gy increase in mean dose of the parotid gland, this is not reflected in the multivariate analysis.

Amifostine

Amifostine has been investigated in order to prevent side effects of chemotherapy and radiotherapy. Most studies on Amifostine in head and neck cancer patients treated with radiotherapy used a daily scheme. However, this scheme is labour intensive, expensive and troubles

patients 5 times a week. In *chapter 6*, the results of a prospective randomised trial are described in which Amifostine in two different administration schedules (three times and 5 times a week) is compared to no Amifostine in head and neck cancer patients treated with radiotherapy. In this study 91 patients were included, 31 were treated with radiotherapy alone, 30 in combination with Amifostine 3 times a week and 30 in combination with Amifostine 5 times a week. Patients treated with Amifostine 5 times a week had a reduced risk of xerostomia as measured with the RTOG late toxicity score system at 6 months after radiotherapy, but not thereafter. Amifostine 3 times a week proved to be less effective. However, considering patient-rated xerostomia as an endpoint, less deterioration was seen with Amifostine, with no difference between the two administration schedules. No benefit was observed of Amifostine on acute toxicity as measured with the RTOG acute toxicity score system. Also no effect was seen on patient-rated sticky saliva.

An important problem encountered in this study was the reduced compliance due to toxicity of Amifostine, in particular nausea and vomiting. A total of 24 patients (28%) discontinued Amifostine before the end of radiotherapy. Though toxicity scores were in the lower range and were considered mild, for many patients nausea and vomiting complaints were a serious burden, even after adjustment of the anti-emetic regimen. Oral correction of hydration status did not reduce nausea sufficiently in all patients. Less frequent observed reasons for discontinuation were allergic skin reactions and non-Amifostine realted hypotension.

Xialine®

In *chapter 7*, the results of a pilot study with Xialine®, a saliva substitute on a xanthan base, are described. In this prospective, placebo-controlled double-blinded trial with a cross over design 30 head and neck cancer patients with xerostomia were included. They were at least 3 months after radiotherapy and it was estimated that at least 75% of their parotid glands had received 50 Gy or more. Though Xialine® appears to improve problems with speech and 'taste and smell', the global QoL in patients with xerostomia resulting from radiation therapy for head and neck cancer was decreased to almost the same level with Xialine® as with placebo.

Chapter 8 contains the general discussion and conclusion of this thesis.

Nederlandse Samenvatting

Bestralingsgeinduceerde droge mond bij hoofdhals-kankerpatienten

Samenvatting

In *hoofdstuk 1* is een overzicht gegeven van een droge mond (xerostomie) veroorzaakt door bestraling, de relatie ervan met bestralingsparameters, de methodes om xerostomie vast te stellen, de relatie ervan met kwaliteit van leven en onderzoek naar behandeling en preventie. Xerostomie is een belastende en moeilijk behandelbare bijwerking van bestraling van patiënten met hoofd-halstumoren en komt ondanks vele inspanningen nog steeds veel voor.

Kwaliteit van leven

Speeksel speelt een belangrijke rol in het dagelijks leven. Er wordt daarom meestal aangenomen dat verminderde speekselproductie effect heeft op kwaliteit van leven. In *hoofdstuk 2* zijn de resultaten gepresenteerd van een prospectief onderzoek naar het effect van xerostomie op kwaliteit van leven. In dit onderzoek zijn de zgn. RTOG-criteria voor late toxiciteit gebruikt als maatstaf voor xerostomie. Ten eerste toont dit onderzoek aan dat xerostomie door bestraling een significant effect heeft op kwaliteit van leven en op xerostomie-gerelateerde dimensies van kwaliteit van leven. Bij toenemende xerostomie werd een afnemend functioneren waargenomen, en bovendien een toename van klachten van slapeloosheid en vermoeidheid. Dit effect is sterker bij vrouwen en jongere patienten. Verder blijkt dat ofschoon de incidentie van xerostomie in de loop der tijd afneemt, het effect van een droge mond op kwaliteit van leven juist toeneemt.

Bestralingsparameters

De meeste onderzoeksresultaten naar xerostomie veroorzaakt door bestraling zijn voornamelijk gericht op het functioneren van de glandulae parotideae. Speeksel wordt echter ook door andere speekselklieren geproduceerd en bestraling van deze andere speekselklieren kan het risico op het ontstaan van xerostomie beïnvloeden. In *hoofdstuk 3* is de relatie beschreven tussen de gemiddelde dosis op de glandulae parotideae, de glandulae submandibulares en de kleine speekselklieren in de mondholte, en het risico op het ontstaan van xerostomie en plakkerig speeksel veroorzaakt door bestraling zoals ervaren door de patiënt. Zowel de gemiddelde dosis op de glandulae parotideae als de gemiddelde dosis op de glandulae submandibulares beïnvloeden het risico op het onstaan van subjectieve klachten van matige of ernstige xerostomie. Dit risico, als een functie van de gemiddelde dosis op de glandulae parotideae,

wordt beïnvloed door de gemiddelde dosis op de glandulae submandibulares; met andere woorden, als de gemiddelde dosis op de glandulae submandibulares wordt verhoogd volstaat een lagere gemiddelde dosis op de glandulae parotideae om dezelfde mate van xerostomie te veroorzaken. De gemiddelde dosis op de mondholte heeft geen significant effect. Plakkerig speeksel als waargenomen door de patiënt hangt voornamelijk samen met de dosis op de glandulae submandibulares, en na verloop van tijd treedt enige verbetering op.

De meeste onderzoeken naar de relatie tussen bestraling en xerostomie betreffen patiënten die beiderzijds op de hals bestraald zijn. Bij sommige patiënten kan de bestraling echter worden beperkt tot de eenzijdige hals, zonder dat dit een negatief effect heeft op de locoregionale controle, bijvoorbeeld bij een T1- of T2-tonsiltumor. In *hoofdstuk 4* is het verband beschreven tussen de gemiddelde dosis in de speekselklieren en xerostomie bij eenzijdig bestraalde patiënten, in vergelijking met dubbelzijdig bestraalde patiënten. Het risico op gematigde of ernstige xerostomie of plakkerig speeksel als waargenomen door de patiënt is significant groter na bilaterale bestraling in vergelijking met unilaterale bestraling. Na eenzijdige bestaling op de hals verbetert xerostomie of plakkerig speeksel als waargenomen door de patiënt tot de uitgangswaarde. De kans op matige of ernstige xerostomie wordt niet alleen bepaald door de gemiddelde dosis op de glandulae parotideae, maar ook door de gebruikte techniek. Wanneer de individuele speekselklieren in ogenschouw worden genomen blijkt de gemiddelde dosis op de contralaterale glandula parotidea de enige relevante factor te zijn in de kans op gematigde of ernstige xerostomie als waargenomen door de patient. De gemiddelde dosis op de mondholte en die op de glandulae submandibulares zijn niet significant.

Gecombineerde behandeling

In *hoofdstuk 5* is het effect beschreven van gecombineerde behandeling, in casu chemotherapie en radiotherapie, op de kans op xerostomie en plakkerig speeksel veroorzaakt door bestraling als waargenomen door de patiënt. Er kwamen 146 patiënten in aanmerking voor dit onderzoek, waarvan er 92 werden bestraald en 54 werden behandeld met chemotherapie en radiotherapie. Uit dit onderzoek blijkt dat de toegevoegde chemotherapie de kans op xerostomie voor bestraalde patiënten niet significant vergroot. Alleen de gemiddelde stralingsdosis op de glandulae parotideae is significant. Niettemin lijkt een univariate analyse naar

behandelingsarm aan te tonen dat chemotherapie enigszins belangrijk is: patiënten in de groep met gecombineerde behandeling hebben een hoger relatief risico (een hogere risico per 1 Gy verhoging van de gemiddelde dosis op de glandulae parotideae); dit is niet terug te vinden in de multivariate analyse. Er is ook geen effect van toegevoegde chemotherapie te zien op de kans op plakkerig speeksel.

Amifostine

Er is onderzoek gedaan naar het gebruik van Amifostine om de bijwerkingen van chemotherapie en bestraling te voorkomen. In de meeste onderzoeken naar Amifostine voor bestraalde patiënten met hoofd-halstumoren wordt een dagelijks regime gebruikt. Dit is echter arbeidsintensief, duur en belastend voor de patiënten. In *hoofdstuk 6* worden de resultaten van een prospectief gerandomiseerde studie gepresenteerd waarin een vergelijking wordt gemaakt tussen twee verschillende toedieningsfrequenties (drie keer en vijf keer per week) en geen toediening van Amifostine bij patiënten met hoofd-halstumoren die een bestralingsbehandeling ondergingen. Aan dit onderzoek deden 91 patiënten mee, 31 werden alleen bestraald, 30 in combinatie met drie keer per week Amifostine en 30 in combinatie met vijf keer per week. Patienten die vijf keer per week Amifostine kregen hebben volgens de RTOG-criteria voor late toxiciteit een verminderd risico op xerostomie gemeten op zes maanden na de bestraling, maar daarna niet meer. Drie keer per week Amifostine blijkt minder effectief te zijn. Wanneer xerostomie als waargenomen door de patiënt echter als eindpunt wordt genomen zijn er minder klachten van xerostomia met Amifostine dan zonder, waarbij geen verschil is geconstateerd tussen de twee toedieningsschema's. Amifostine heeft geen gunstig effect op acute bijwerkingen. Verder is geen er geen effect op plakkerig speeksel waargenomen.

Een belangrijk probleem is de verminderde compliance vanwege de bijwerkingen van Amifostine, met name misselijkheid en braken. In totaal 24 patiënten (28%) stopten voortijdig met Amifostine voor het einde van de bestralingsserie. Ofschoon de bijwerkingen mild waren, bleken misselijkheid en braken een zware belasting voor veel patiënten, zelfs na aanpassingen aan de anti-emetische therapie. Orale rehydratie was niet altijd voldoende effectief om de misselijkheid tot een voor de patiënt aanvaardbaar niveau te verminderen. Ook werd de behandeling soms gestaakt wegens allergische huidreacties en niet-Amifostinegerelateerde hypotensie.

Xialine®

In *hoofdstuk 7* worden de resultaten uiteengezet van een pilot-studie met Xialine®, een speekselvervanger op basis van xanthan. Aan dit prospectieve dubbelblinde placebo-gecontroleerde crossover-onderzoek deden 30 patiënten met een hoofd-halstumor mee. De bestraling was ten minste 3 maanden geleden en geschat werd dat ten minste 75% van hun glandulae parotideae minstens 50 Gy bestraling had gekregen. Ofschoon Xialine® problemen met spraak en 'smaak en reuk' enigszins verhelpt, vermindert de kwaliteit van leven van patiënten met xerostomie als gevolg van bestraling voor hoofd-halstumoren bijna evenveel met Xialine® als met een placebo.

In *hoofdstuk 8* staat de algemene discussie en de conclusie van dit proefschrift.

Dankwoord

Dankwoord

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Daarnaast zijn er nog vele anderen die hebben bijgedragen aan het tot stand komen van dit proefschrift.

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